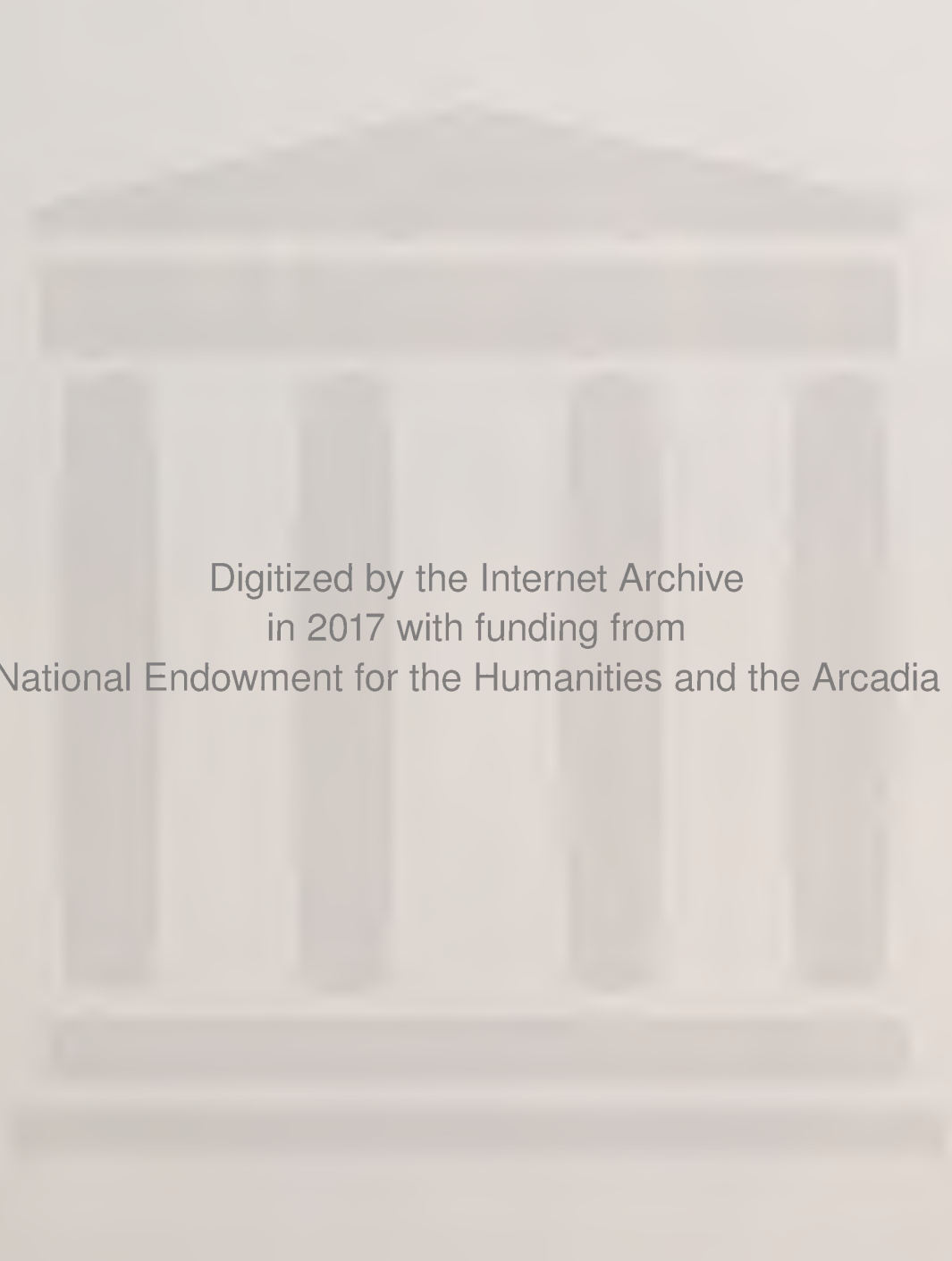


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BOLETIN

ASOCIACION MEDICA DE PUERTORICO

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NOTICIAS

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NUM. 1

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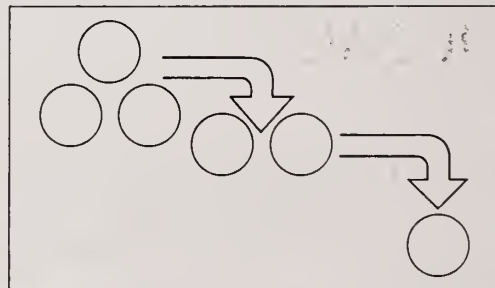
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*Sellers EM: *Drug Metab Rev* 8(1):5-11, 1978



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Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

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Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Medical Treatment Can Help Curb Acne

Acne Cure Elusive

Something can be done about acne. But beware the promise of a guaranteed cure. There are many, many approaches to treating the unsightly blackheads and pimples. But no one can promise a cure.

Acne is a common skin problem that affects most people to a varying degree and for a varying period during the teen years. But adults also can have acne.

Waiting to outgrow acne can be a serious mistake. Treatment by a physician can prevent the development of pitted scars and may improve appearance.

An American Medical Association pamphlet points out that basic research on the causes of acne links its occurrence to the biological changes that take place as young people mature. While acne usually clears after several years even if untreated, much can be done to minimize disfigurement. Treatment is a continuing process if the disorder is to be controlled successfully.

Acne is not caused by dirt,

but the sufferer may be told to wash frequently to cleanse the face of skin oils and hold down the formation of blackheads and pimples. Acne is not primarily a dietary disease, and authorities vary on the importance of diets in control of acne. One thing is certain: Following the strictest diet will not, by itself, clear your skin. Some people, however, find that their acne becomes worse when they eat small amounts of certain foods, particularly chocolate and fats.

Many nonprescription creams and lotions are available at drugstores. These may be of some benefit. Be certain to read the instructions and follow them.

Your doctor may make specific dietary suggestions. He probably will prescribe a preparation to be applied to your skin to help reduce oiliness and produce mild peeling. He may open inflamed lesions, and he may remove blackheads. Your doctor will most certainly warn you against picking, scratching, popping and squeezing.

Antibiotics often are prescribed for inflammatory acne. They reduce the bacteria in the skin. Anti-inflammatory cortisone-like drugs sometimes are prescribed.

No matter what the treatment, proper skin care by the individual is highly important.



October, 1980
Frank Chappell
Science News Editor
AMA

BOLETIN

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 - * Review Article: Recent Advances in Vasodilator Therapy.
Part I: Physiologic Correlations 3
*Juan M. Aranda, MD, Esteban Linares, MD, Edgardo Hernández
López, MD, Guillermo Cintrón, MD and Samuel Song, MD*

In this issue of the Boletín, we review the basic factors which govern the hemodynamic responses obtained after the administration of vasodilator agent. As a general principle, venodilators should be used when signs and symptoms of pulmonary congestion predominate, (orthopnea, paroxysmal nocturnal dyspnea); on the other hand arteriolar dilators are not useful in those clinical conditions characterized by low cardiac output since they decrease arteriolar resistance with a minimal decrease in venous return and left ventricular filling pressure. An extremely important concept is emphasized; if not properly used both venodilators and arteriolar dilators may cause further impairment of left ventricular function. Our readers are referred to Figure 1 in this article. It is clearly seen that if venodilators are administered when the wedge or left ventricular filling pressure is below 15 mm Hg, decreases in pressure will be accompanied by a decrease in cardiac output. This and other concepts should be carefully studied by all physicians that care for and follow up patients with congestive heart failure.

- * Diferenciales en Mortalidad Por Sexo en Puerto Rico 11
Annette B. Ramírez de Arellano

En este artículo, la autora aplica el indicador "años de capacidad potencial perdida" (ACP) para evaluar el efecto en que la mortalidad prematura afecta diferencialmente a los hombres de las mujeres. Aunque en Puerto Rico, las mujeres se enferman más que los hombres, la tasa de mortalidad masculina es 1.5 veces mayor que la femenina. Las causas de muerte más comunes en los hombres puertorriqueños en el año 1978 fueron las enfermedades del corazón, cáncer y las enfermedades cardiovasculares. Sin embargo este orden se altera significativamente cuando se usa el índice o el indicador ACP. Las enfermedades cardiovasculares sufren un descenso considerable reflejando el hecho de que estas causas de muerte son selectivas de la población en edades avanzadas, en las cuales la capacidad potencial necesariamente disminuye. Concluye la autora que más de la mitad de los años de capacidad productiva perdidos son atribuibles a los accidentes, homicidios y suicidios. Si esta conclusión es cierta, implica entonces que las intervenciones estrictamente médicas son relativamente ineficientes en prolongar la vida productiva del hombre puertorriqueño. A mi entender, este concepto debe despertar interés y comentarios de todos aquellos relacionados a la planificación de salud y servicios médicos en nuestra isla. El Editor.

- * Sobre las Influencias Ambientales Relevantes a la Prevención del
Desarrollo Precoz de la Catarata Senil 18
Manuel N. Miranda, MD y Sixto García Castiñeiras, MD, PhD

En este artículo Miranda y García Castiñeiras presentan datos epidemiológicos que su-

gieren que el factor geográfico detectable en el desarrollo de la catarata senil depende de los efectos ambientales sobre la temperatura del lente cristalino. Dicen los autores que existe una relación negativa entre el promedio anual de temperatura y la edad promedio del comienzo de la presbicie y la catarata senil. En otras palabras parece ser que en regiones frías la edad promedio del comienzo de estas condiciones es mucho mayor en regiones frías que en regiones cálidas. En vista de esta posible correlación, los autores recomiendan el uso de espejuelos que disminuyan la entrada al ojo de radiaciones con efecto térmico.

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TUBERCULOSIS Y LA QUIMIOTERAPIA DE CORTA DURACION

Uno de los dolores de cabeza para los clínicos envueltos en el manejo de pacientes con tuberculosis ha sido el de mantener al paciente en quimioterapia diaria, continúa por 18 o 24 meses. Por más fiel que sea el paciente en seguir las instrucciones del galeno, siempre habrá ciertas dosis que se omitan involuntariamente. En el caso del paciente alcohólico o penitenciario, el problema de cumplimiento de la ingesta de estas drogas se acentúa aún más. Raro es el individuo en estos últimos dos grupos que cumple a cabalidad con el tratamiento prescrito. Como consecuencia son focos potenciales para la infección de otras personas.

Con el advenimiento del rifampin, una verdadera revolución ha surgido en el manejo de la tuberculosis. Su uso combinado con isoniazida ha permitido la introducción en el occidente de una terapia mucho más efectiva y de duración corta. En el pasado era necesario utilizar una combinación de tres drogas en el tratamiento de lesiones pulmonares que contenían grandes poblaciones de bacilos. En muchos casos los riesgos de fracaso y reactivación de la enfermedad eran altos. Para evitar esto, el médico debía asegurarse que el paciente seguía el tratamiento por 18 a 24 meses consecutivos, y desafortunadamente muchos pacientes encontraban este modo de terapia intolerable.

Para entender cómo el tratamiento de corta duración es tan efectivo, tenemos que repasar ciertas características biológicas del bacilo tuberculoso. La primera de estas características es el requisito de tener oxígeno abundante para crecer y multiplicarse. El bacilo es un organismo estrictamente aeróbico y aquí la explicación por lo cual hay tantos organismos en la caverna tuberculosa. El ambiente hiperóxico en estas lesiones favorecen su amplio desarrollo.

Otra idiosincracia de este organismo es la de su lento tiempo de replicación. Se calcula éste en aproximadamente 20 horas. Si comparamos esta tasa de desarrollo con la de la "E. Coli" o el "Staph Aureus" que es de 20 minutos, podemos entender por qué la quimioterapia de la tuberculosis debe ser más prolongada que la de las bacterias comunes.

La tercera propiedad importante de estas micobacterias es la alta tasa de mutaciones a formas resistentes a drogas. En un cultivo dado de estos organismos se calcula que la resistencia a la isoniazida es de 10^{-5} , a la estreptomycin, 10^{-6} y al rifampin 10^{-7} . Por lo tanto es fácil seleccionar cepas resistentes con el uso clínico de solo una droga. Sin embargo, si utilizamos dos drogas, y estas dos son altamente bactericidas la incidencia de organismos resistentes no va a ser clínicamente notable.

En el transcurso de una infección tuberculosa pulmonar se pueden identificar tres poblaciones distintas de micobacterias. La primera, son aquellas que están creciendo en el pH neutral del material caseado que cubre la caverna. La segunda población, es la que está creciendo intracelularmente dentro de los macrófagos. La tercera consiste de organismos que están localizados y creciendo en el material caseado endurecido en ciertas áreas fuera de las cavernas. Estos últimos organismos son muy importantes en el diseño de cualquier regimen quimioterapéutico, ya que hay que tener en cuenta que estos están creciendo muy lentamente en estas dos últimas poblaciones.

Cualquier combinación de drogas para uso de corta duración, por ende, tiene que ser efectiva con cada una de estas tres poblaciones, cuyas tasas de metabolismos son obviamente diferentes. Adicionalmente, las drogas seleccionadas deben actuar rapidamente y ser completamente bactericidas. Afortunadamente este es el caso con isoniazida y rifampin.

Existe una gran cantidad de data experimental que demuestra como Isoniazida usada en dosis tan altas como 25 mg/kg o en dosis tan bajas como 5 mg/kg en combinación con Rifampín (25 mg/kg) es capaz de cambiar el status de un ratón positivo a negativo en menos de seis meses.

Hay una gran proliferación de posibles combinaciones y duraciones de regímenes de corta duración utilizando el rifampín y la isoniazida, dos de las drogas más micobactericidas que existen al presente. Uno de estos programas que mejores resultados ha dado, quizás por su simplicidad, es el regimen usado por los doctores Asim K. Dutt y William Stead, ambos del Programa de Control de Tuberculosis del estado de Arkansas. El regimen de Arkansas consiste de la administración de Rifampín, 600 mg y de isoniazida, 300 mg por el primer mes; seguido por Rifampín 600 mg e isoniazida, 15 mg por kg de peso (900 mg en la mayoría de los pacientes), dado dos veces en semana por los restantes ocho meses para un total de noventinueve dosis en un período total de nueve meses. Al momento de la publicación de sus resultados, el grupo de Arkansas tenía en tratamiento 650 pacientes. El 98 por ciento de estos pacientes tuvieron respuestas excelentes. El 80 por ciento convirtieron sus esputos de positivos a negativos en dos meses. Solo el 1 por ciento de estos pacientes han tenido relapsos de su enfermedad. Todos y cada uno de estos fracasos ocurrieron dentro de los seis meses subsiguientes al cese de terapia y todos los organismos mantuvieron su susceptibilidad a isoniazida y rifampín.

Los resultados arriba descritos son altamente prometedores. En Puerto Rico con nuestros escasos recursos económicos, y nuestra alta prevalencia de tuberculosis, comparados con la de Estados Unidos, este regimen bien podría ser utilizado para bajar costos y para aumentar las curas completas requeridas para el control óptimo de esta enfermedad. Ahora que los sanatorios y la gran mayoría de las unidades públicas para el control de la tuberculosis han sido eliminadas, nuestros pacientes están siendo atendidos en hospitales públicos y comunitarios. Necesitamos hacer conscientes a los médicos primarios de la disponibilidad de estos regímenes modernos, que proveen control rápido y efectivo del bacilo, para su pronta erradicación en nuestra Isla.

Referencias

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REVIEW ARTICLE:

RECENT ADVANCES IN VASODILATOR THERAPY PART I: PHYSIOLOGIC CORRELATIONS

Juan M. Aranda, MD, Esteban Linares, MD, Edgardo Hernández
López, MD, Guillermo Cintrón, MD and Samuel Song, MD

Summary: The hemodynamic responses obtained after the administration of vasodilator agents in patients with congestive heart failure, will depend on their relative effects on arterioles and veins. Those that predominantly cause arteriolar dilatation will produce an increase in cardiac output without significant changes in pulmonary wedge or left ventricular filling pressure. Agents that mediate venodilatation will decrease pulmonary capillary wedge pressure without significant increases in cardiac output. Their hemodynamic effects when used in patients with acute infarction and left ventricular failure will depend on the initial level of left ventricular filling pressure. Hemodynamic monitoring (pulmonary capillary wedge pressure, cardiac output and blood pressure) should be used, specially in the acute situations, to assess the effects of this mode of therapy.

Resumen: La respuesta hemodinámica obtenida de la administración de agentes vasodilatadores a pacientes con fallo congestivo cardíaco va a depender de su efecto relativo en las arteriolas y venas. Aquellos vasodila-

tadores que predominantemente causan dilatación arteriolar, aumentan el débito cardíaco sin cambios significativos en la presión de cuña pulmonar. Aquellos que son vasodilatadores venosos, disminuyen la presión de cuña pulmonar sin causar cambios significativos en el débito cardíaco. Los efectos hemodinámicos en pacientes con infarto agudo del miocardio y decompensación cardíaca van a depender del valor o nivel inicial de la presión telediastólica del ventrículo izquierdo. El rastreo hemodinámico es indispensable en situaciones agudas, para determinar los efectos hemodinámicos de este tipo de terapia.

Congestive heart failure is still one of the most serious illnesses in man and a frequent cause of disability and death. The cardiac pathophysiology and the clinical manifestation have been extensively studied, but some aspects of the pathophysiology, specially the changes in the peripheral circulation, venous pressure and venous tone have just been recently emphasized (1-4).

The traditional therapy for congestive heart failure has relied upon digitalis and diuretics to reduce pulmonary venous pressure and re-establish cardiac reserve. However, the mechanical performance of the heart is dependent not only on the functional ca-

capacity of the muscle (contractility) and the length of the muscle fiber at end diastole (preload), but also on forces which oppose ventricular ejection (afterload) (2).

It has been extensively documented that peripheral blood vessels are constricted and that venous tone is high in patients with congestive heart failure (3). Although peripheral vessel dilatation has been used for many years to treat hypertensive heart failure, it has only been in the past 5 years that the use of this mode of treatment has become popular in the therapy of normotensive heart failure.

The objective of this article is to review the methodology, clinical results and limitations of this mode of therapy.

Peripheral Circulatory Determinants of Cardiac Function

Congestive heart failure is an abnormal hemodynamic state associated with enhanced sympathetic tone, high levels of circulating catecholamines and increased activity of the renin angiotensin system (3-4). These factors are combined to increase systemic vascular resistance which in turn increases impedance to left ventricular ejection, leading to further impairment of left ventricular performance. It has therefore become apparent that peripheral circulatory factors may induce major changes in left ventricular function. Moreover, these changes assume greater significance in the clinical setting of congestive heart failure.

The principal peripheral vascular determinants of left ventricular function are: (5)

1. Venomotor changes - these prominently alter venous return or

ventricular preload. The venous return or ventricular preload is the major determinant of the end diastolic fiber length.

2. Arterial resistance - it is the main determinant of the impedance to left ventricular ejection and regulates ventricular afterload or the ventricular tension developed during ventricular contraction.

PRE LOAD: Ventricular preload can be modified by interventions that bring about an absolute change in intravascular volume. (5) This change in intravascular volume may be brought about by redistribution of intravascular volume, by altering end ventricular diastolic volume or by varying ventricular diastolic compliance. Preload may thus be reduced by diuresis, venodilatation, enhancement of ventricular contractility and increased ventricular stiffness (3).

AFTER LOAD: The load or wall tension that the left ventricle must develop to eject blood into the aorta, constitutes ventricular afterload (3-4). The two principal determinants of ventricular afterload are the systolic pressure developed during left ventricular contraction and the radius of the left ventricle at the onset of contraction. In turn, systolic pressure is related to the impedance to blood flow in the aorta, while the left ventricular radius is directly related to the left ventricular volume.

AORTIC IMPEDANCE: Left ventricular outflow impedance is governed primarily by the compliance of the large arteries (relation of pressure to flow) and by total peripheral vascular resistance which is determined principally by the radius or cross

sectional area of the systemic arterial bed. Blood viscosity and intra-arterial volume may also alter aortic impedance. Of all the factors regulating aortic impedance, systemic arteriolar resistance is the most important and the variable most subjected to modification by vasodilating agents (3-5).

CLINICAL IMPLICATIONS: In the presence of impaired ventricular performance, elevation of ventricular afterload due to an increased sympathetic tone and arteriolar resistance results in a decreased stroke volume and ejection fraction with consequent elevation of left ventricular filling pressure. As a result of the increased afterload, intramyocardial wall tension increases in an attempt to maintain an adequate stroke volume. This in turn requires an increase in myocardial energy (or oxygen) consumption.

As a consequence of the diminished stroke volume and ejection fraction, there is an increase in venous tone which enhances venous return in an attempt to increase diastolic fiber length and cardiac output.

This rise in myocardial energy demands leads to additional impairment of ventricular function, which in turn causes greater sympathetic induced elevation of arteriolar resistance. Systemic vasodilatation, a mode of therapy that produces decreases in preload and afterload may interrupt this harmful chain of events.

Relationship Between Diastolic Fiber Length and Cardiac Output; The Ventricular Function Curve

Figure 1A represents the function of the right or left ventricle related to changes in end diastolic volume. The vertical axis represents some measure of ventricular per-

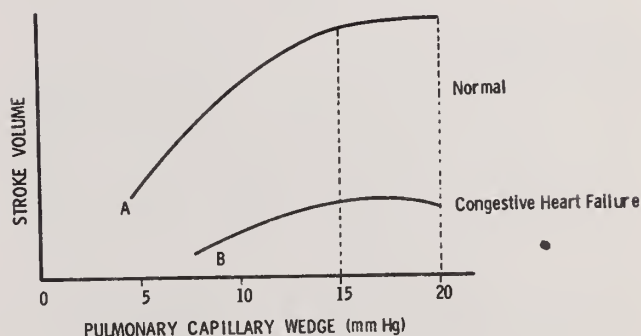


Figure 1 (A & B): This ventricular function curve presents the relationship between stroke volume (or any other measurement of ventricular performance) as a function of pulmonary capillary wedge pressure (or any other measurement of preload). Note that as the filling pressure increases, the stroke volume improves up to a filling pressure of 15 mm Hg. Further increases in wedge pressure are not accompanied by increases in stroke volume, but produce pulmonary vascular congestion.

formance such as stroke volume, cardiac output or stroke work (stroke volume x peak systolic pressure). In clinical practice, a segment of the ascending level is obtained by determining cardiac output at different end diastolic volumes. Since it is technically difficult to measure left ventricular end diastolic volume, left ventricular end diastolic pressure is utilized as an estimation of end diastolic fiber length.

In order to measure left ventricular end diastolic pressure (LVEDP) directly, one must place a catheter in the left ventricle. On the other hand, it is simpler to use a balloon-tip flotation catheter (Swan-Ganz catheter) to measure pulmonary wedge pressure. This pressure indirectly reflects left atrial pressure

which is a measure of left ventricular end diastolic pressure.

The curve consists of an ascending limb on which increases in end diastolic pressure produce elevation of stroke volume, cardiac output and cardiac performance. The ascending limb is terminated at a level of end diastolic pressure that produces no further increases in stroke volume. As one continues to increase LVEDP, the curve flattens out.

In normal subjects, the apex of the ventricular function curve (highest stroke volume observed) is usually found at a LVEDP of about 12-14 mm Hg (6-7), whereas in patients with an acute myocardial infarction the optimal level of filling pressure has been reported as 14-18 mm Hg. Further increases in pulmonary capillary wedge pressure are not accompanied by increased cardiac performance, but may eventually produce pulmonary vascular congestion.

In patients with congestive heart failure or acute myocardial infarction, situations of decreased myocardial contractility, the entire ventricular function curve shifts downward and to the right (Figure 1B). The ascending limb is prolonged and less steep and the descending limb has a depressed slope.

Current evidence suggests that the failing human heart does not operate on the descending limb of the ventricular function curve for prolonged periods of time (8) since decreases in preload (or left ventricular end diastolic pressure) have not increased cardiac output or stroke work (9-10). Finally, it should be pointed out that any alteration in preload is indicated by changes of position on the same curve and that alterations of contractility are documented by shifts of the entire ventricular function curve as shown in Figure 1 (A, normal ventricular function curve, B, ventricular function curve in a state of decreased contractility).

CLINICAL IMPLICATIONS: Considering the relationship between stroke volume and filling pressure, it can be readily visualized that the effects of a venodilator on cardiac function will depend on the initial level of left ventricular filling pressure at the time the agent is administered. If the agent is administered when the filling pressure is normal, the reduction in filling pressure caused by peripheral blood pooling, will lower the stroke volume. As the ventricle moves down the ascending limb of its function curve (Figure 1B) in order to maintain the cardiac output (cardiac output=stroke volume x heart rate), there will be an increase in heart rate to balance the reduction in stroke volume caused by the vasodilator. However, if the peripheral venodilating agent is administered when the LVEDP is elevated (over 15 mm Hg), the reduction in filling pressure will occur in the flat portion of the ventricular function curve and will not be accompanied by a reduction in stroke volume. This will occur as long as the LVEDP does not fall below 15 mm Hg. The use of venodilating agents, under these circumstances will improve the symptoms of dyspnea, orthopnea and fatigue associated with elevations in pulmonary capillary wedge pressure and pulmonary congestion. From these observations it can be stated that agents that decrease preload or filling pressure relieve symptoms of pulmonary congestion, but do not cause any significant increase in cardiac output.

It is of utmost importance not to administer venodilator agents to patients with normal or low filling pressure and limited cardiac reserve.

Mechanism of Action of Ventricular Afterload Reducing Agents

The most important mechanism by which vasodilators increase cardiac output is by reducing ventricular afterload. Since it has been very difficult to quantitate ventricular afterload in the human heart, (it involves measurement of intraventricular pressure, wall thickness and fiber direction) other approximations of afterload have been used in clinical practice, mainly aortic pressure and aortic impedance.

The aortic pressure has an extremely important and direct influence on ventricular afterload, since it represents the pressure that must be developed by the heart before the aortic valve is opened and blood is ejected into the aorta. However, in some situations aortic pressure does not reflect changes in cardiac function produced by vasodilator drugs. If it is remembered that blood pressure is dependent on cardiac output and systemic vascular resistance ($BP = CO \times SVR$), it is readily visualized that an arteriolar vasodilator may reduce the systemic vascular resistance and increase the cardiac output by the same magnitude. Under these circumstances, the blood pressure will remain unchanged even though the cardiac output has been significantly increased. This illustrates two basic concepts related to the use of arterial vasodilators; a) blood pressure determination is not the best parameter available to measure ventricular afterload; b) the therapeutic effects of vasodilators cannot be assessed by how much they decrease arterial blood pressure. It may be possible to achieve maximal beneficial hemodynamic effects (decrease pulmonary wedge pressure, increase cardiac output) with a minor or no reduction in arterial pressure.

A more accurate measurement of after-

load is the systemic vascular resistance. As was previously discussed, aortic impedance is the instantaneous relation between pressure and flow in the aorta during ejection. Impedance is directly proportional to the aortic pressure and inversely proportional to aortic flow ($\text{impedance} = \text{pressure} / \text{flow}$). While impedance is the instantaneous relationship between these two factors, resistance is the average of this relationship throughout the cardiac cycle. Multiple well controlled studies have shown that decreases in aortic impedance brought about by decreases in systemic vascular resistance is the principal mechanism by which arterial vasodilators reduce ventricular afterload and increase cardiac output (11-12).

An important concept to remember is that in acute situations in patients with severe congestive heart failure, an objective parameter other than the arterial pressure should be followed in order to determine the effects of vasodilator therapy.

Do Vasodilator Agents Have a Direct Inotropic Effect on the Myocardium?

As a rule, vasodilator agents do not have any direct inotropic effects on the myocardium. Under some circumstances there may be reflex sympathetic effects mediated through the baroreceptor mechanism. This is shown by the fact that a decrease in arterial pressure with a normal filling pressure may be accompanied by an increase in sympathetic tone to the heart which will result in an increase in heart rate and contractility. However, this effect does not occur in patients

with congestive heart failure and increased filling pressure.

Recently, Khatri and co-workers (13) performed several experiments which showed that intracoronary arterial injection of hydralazine in small doses insufficient to cause systemic effects or decrease in blood pressure, led to an increase in the contractility of the myocardial segment perfused by the artery. The contractility of the segments not perfused did not change. He proposed that the direct inotropic effect of hydralazine was mediated through the release of histamine which liberated catecholamines into the myocardium.

Other Mechanism by which Vasodilators Improve Myocardial Performance

Reduction in segmental ischemia is another mechanism by which vasodilators may improve performance in patients with coronary artery disease. In patients with coronary artery disease, an area with myocardial ischemia represents an imbalance between oxygen demand and supply. Oxygen supply is limited by the severity of the coronary arterial stenotic lesion. Vasodilator therapy may decrease one or more of the four most important determinants of myocardial oxygen demand; arterial pressure, heart rate, heart size and contractile state. By decreasing one of these determinants, oxygen demand is reduced, leading to a reduction in segmental ischemia.

Vasodilators will reduce preload and filling pressure, causing a decrease in end systolic volume and heart size. The decrease in arterial pressure caused by these agents will also decrease myocardial oxygen demand. In general, in patients with congestive heart

failure, there will not be a compensatory increase in heart rate as preload and arterial pressure are decreased. Since these agents do not have a direct effect in myocardial contractility, this factor will not be altered.

Considering Khatri's report on the direct effect of hydralazine on myocardial contractility, further studies are needed to clarify his observations.

Recent studies (14) have shown that vasodilator agents have a direct beneficial effect on the compliance of the left ventricle. This beneficial effect is another mechanism through which these agents improve cardiac performance. The compliance of the left ventricle is the instantaneous relationship that exists between changes in intraventricular pressure and ventricular volume (Figure 2). Changes in pressure (ΔP) are always accompanied by changes in ventricular volume (ΔV). Decreased left ventricular compliance (decrease $\Delta V/\Delta P$), indicates that as left ventricular pressure increases there is less than expected or a minimal increase in left ventricular volume. As this occurs, there is a reduction in ventricular performance. Increase in left ventricular compliance (increase $\Delta V/\Delta P$) indicates that as left ventricular pressure increases, there is a larger than expected increase in left ventricular volume (Figure 2). Since the left ventricular end diastolic volume is the most important determinant of stroke volume, the larger the volume at a constant filling pressure, the greater the stroke volume and cardiac output (improved ventricular performance). It is thus apparent that agents that cause an increase in ventricular

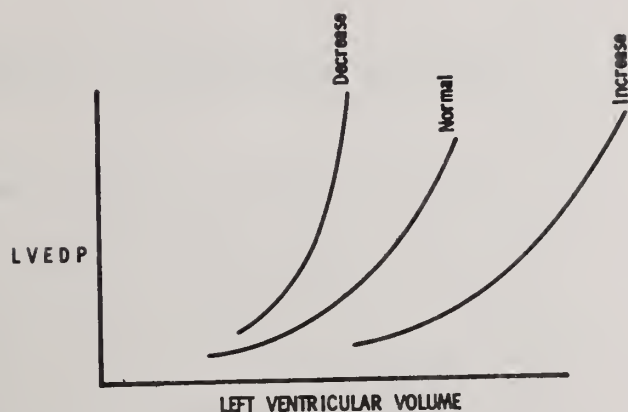


Fig. 2: Relationship between left ventricular volume and left ventricular end diastolic pressure (LVEDP). As LVEDP increases there is a corresponding increase in ventricular volume. In patients with decreased compliance, increases in LVEDP are accompanied by a less than expected increase in ventricular volume. In patients with increased ventricular compliance, at the same level of LVEDP, there is a greater ventricular volume.

compliance could influence the relationship between filling pressure and cardiac output improving cardiac performance. As reported by Parmley et al (14) vasodilator agents can produce an increase in left ventricular compliance probably mediated through an interaction between the right and left ventricle in a confined pericardial space (14). If the vasodilator reduces both arterial and right atrial pressure, it will reduce both left and right end diastolic volumes. The reduction in size of the right ventricular cavity within the stiff pericardial space will permit the more muscular left ventricle to dilate further at the same level of end diastolic pressure. This will increase left ventricular compliance. The greater left ventricular volume will result in an improved cardiac output and cardiac performance.

Conclusions

The hemodynamic responses observed after the administration of vasodilator agents depend on their relative vasodilating effects on arterioles and veins. Those that cause predominant dilatation of peripheral arterioles, produce an increase in cardiac output without significant decrease in pulmonary wedge pressure. Agents that mediate venodilatation will decrease capillary wedge pressure without a significant increase in cardiac output.

Their beneficial hemodynamic effects when used in patients with congestive heart failure, specially if it is associated with an acute myocardial infarction, will depend on the initial level of left ventricular filling pressure (LVEDP). When the LVEDP is less than 15 mm Hg, further reduction in pressure will be accompanied by reduction in stroke volume. Heart rate will increase in an attempt to maintain a normal cardiac output. When LVEDP is elevated (>15 mm Hg), the decrease in LVEDP may be accompanied by slight increased stroke volume and cardiac output without an increase in heart rate. It is strongly recommended to identify the subset of patients that will benefit from vasodilator therapy specially when used in *acute* situations. Hemodynamic monitoring (wedge pressure, cardiac output and blood pressure monitoring) should always be used in the acute situation to assess the beneficial hemodynamic effects of this mode of therapy.

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DIFERENCIALES EN MORTALIDAD POR SEXO EN PUERTO RICO

Annette B. Ramírez de Arellano

Resumen: Los datos sobre las condiciones de salud de la población puertorriqueña indican que, aunque las mujeres se enferman más que los hombres, la tasa de mortalidad masculina es 1.5 veces mayor que la femenina y la esperanza de vida al nacer es siete años mayor para las mujeres que para los hombres. El indicador denominado "años de capacidad potencial perdida" (ACP) revela la medida en que la mortalidad prematura afecta diferencialmente a los hombres; éstos representan más de un 70 por ciento de los ACP perdidos por las principales causas de muerte. El cómputo de los ACP desglosados por sexo también indica cómo varían las causas de mortalidad prematura entre un sexo y otro; los accidentes y los homicidios son las causas más importantes entre los varones, mientras el cáncer y las enfermedades del corazón lo son entre las mujeres. El artículo concluye con las implicaciones de estos hallazgos para las estrategias de salud.

Summary: The data on the health status of the Puerto Rican population indicate that,

although females have greater morbidity than males, the male death rate is 1.5 times that of females and life expectancy at birth among women surpasses that for men by seven years. The indicator "potential years of life lost" (PYLL) reveals the extent to which premature mortality has a differential impact on men; these account for over 70 per cent of all PYLL attributed to the ten major causes of death. The breakdown of PYLL by sex also indicates how the various causes of premature death have a differential impact between one sex and the other; accidents and homicides are the most important causes among men, while cancer and heart disease are the most important among women. The article concludes with the implications of these findings for the design of health strategies.

Introducción

El sexo es frecuentemente una variable determinante en la salud y en la enfermedad. Esto se debe a que el sexo de una persona afecta o condiciona la interacción de los elementos que componen la tríada epidemiológica: el agente, el ambiente y el huésped. Las diferencias en sexo a veces conllevan diferencias biológicas en susceptibilidad o inmunidad a condiciones particulares. En nuestra cultura, las diferencias sexuales también implican diferencias ocupacionales y en estilos de vida, y así

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en el grado de exposición a una variedad de riesgos a la salud. No es sorprendente, por lo tanto, que los hombres y las mujeres muestren diferentes patrones de morbilidad y mortalidad.

Los datos sobre las condiciones de salud de la población puertorriqueña sugieren que, independientemente del indicador utilizado (incidencia de condiciones agudas, prevalencia de condiciones crónicas, frecuencia de consulta médica o días de actividad restringida), las mujeres se enferman más que los hombres (1). No obstante, la tasa de mortalidad general masculina es 1.5 veces mayor que la femenina (7.1 versus 4.8 por cada 1,000 habitantes), y la esperanza de vida al nacer es siete años mayor para las mujeres que para los hombres (77.4 años, en contraste con 70.4) (2). Este artículo se propone examinar estas diferencias más a fondo, utilizando como instrumento de medición los "años de capacidad potencial perdida".

Metodología

El indicador denominado "años de capacidad potencial perdida", (ACP) va dirigido hacia medir la importancia relativa de las diferentes causas de muertes, destacando aquellas que impactan prematuramente (es decir, en edades en que se puede asumir que la víctima ha perdido años de productividad potencial).

Este indicador se basa en una medición de la diferencia entre la edad en que murió una persona y el promedio de años que ésta hubiese vivido de no haber estado expuesta al riesgo de esa muerte. El cómputo del ACP se basa en un método ampliamente difundido y reportado en la literatura (3). Este consiste en multiplicar el número de defunciones en un grupo etario específico por el promedio de años de vida que ese gru-

po viviría. Cuando este cálculo se hace para una causa específica, los productos así obtenidos luego se suman, arrojando así el total de ACP perdidos por esa causa.

Debido a que el ACP le otorga mayor peso a las muertes ocurridas en edades tempranas, este indicador es de utilidad en definir prioridades para la acción preventiva entre diferentes condiciones o grupos poblacionales (4). Por tal razón, el índice de ACP, originalmente desarrollado por el Centro de Estudios del Desarrollo (CENDES) de Venezuela y la Organización Panamericana de la salud (5), se ha popularizado en los últimos años. Entre los países que han utilizado este indicador para evaluar y ponderar sus causas de mortalidad se encuentran Canadá (6) e Israel (7).

En un artículo anterior, la autora computó el ACP para las principales causas de muerte en Puerto Rico en el 1977 (8). Además de replicar la metodología anterior utilizando datos para el año 1978, el actual esfuerzo tiene como objetivo detectar diferencias en el ACP no sólo entre las diferentes causas, sino también en términos de sexo.

Hallazgos

Como muestra la Tabla I, los rangos relativos de las primeras diez causas de muerte se alteran significativamente cuando se usa el índice o la tasa ACP en contraste con las tasas de mortalidad general. Con excepción del cáncer, el cual mantiene el mismo rango independientemente del indicador usado, todas las demás causas modifican su rango. Las enfermedades cerebrovasculares, la diabetes mellitus y la arterioesclerosis sufren un descenso considerable, reflejando el hecho de que estas causas son selectivas de la población en edades avanzadas, en las cuales la capacidad potencial

TABLA I

Rangos de Causas de Muertes, por Indicador Utilizado
Puerto Rico: 1978

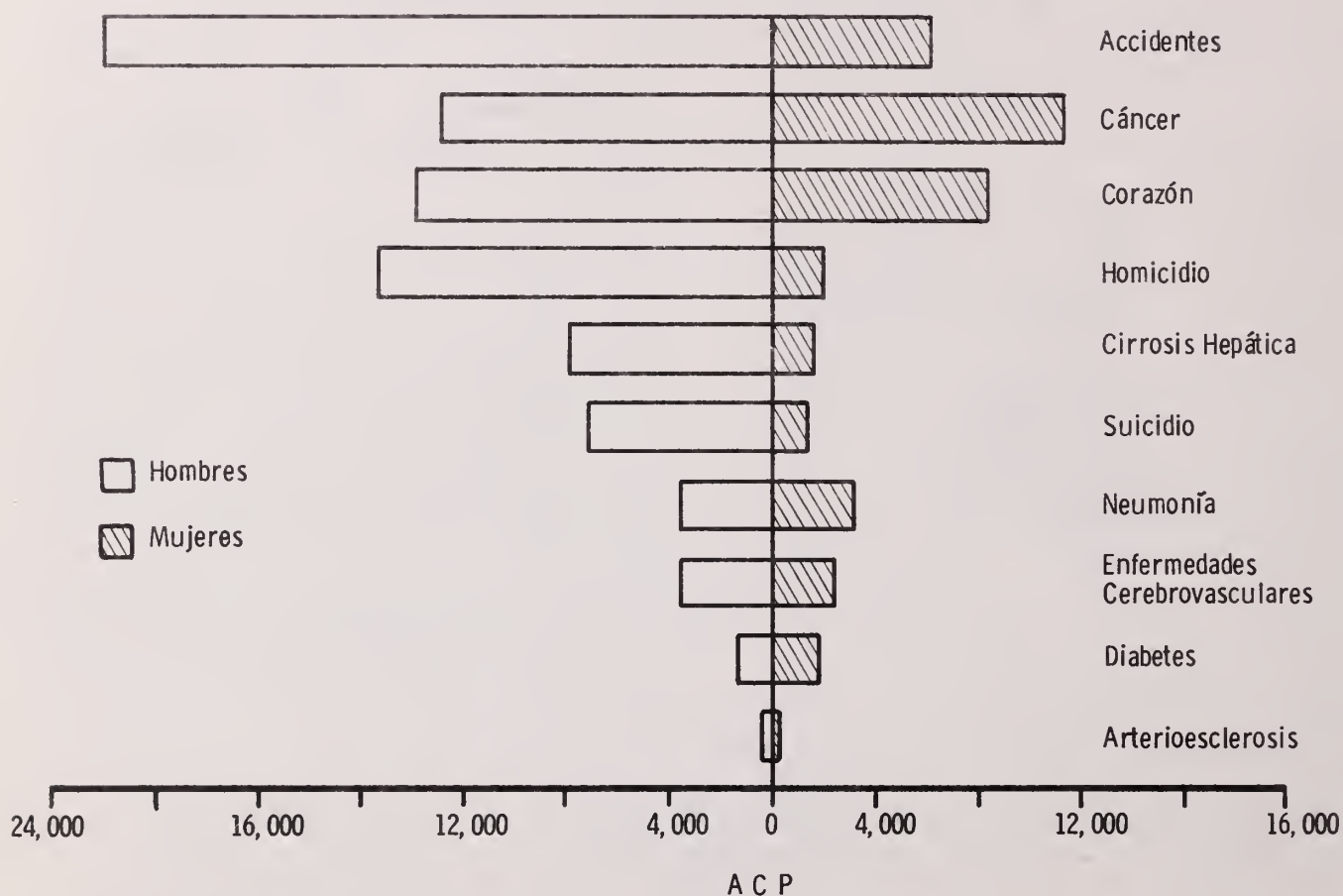
<i>Causa de Muerte</i>	<i>Tasa de Mortalidad</i>	<i>ACP</i>
<i>Enfermedades del Corazón</i>	1	3
<i>Cáncer</i>	2	2
<i>Enfermedades Cerebrovasculares</i>	3	8
<i>Accidentes</i>	4	1
<i>Neumonías</i>	5	7
<i>Diabetes Mellitus</i>	6	9
<i>Arterioesclerosis</i>	7	10
<i>Cirrosis Hepática</i>	8	5
<i>Homicidios</i>	9	4
<i>Suicidios</i>	10	6

TABLA II

Años de Capacidad Productiva Perdidos entre las Edades de 1 a 70 Años, Por Causa y Sexo
Puerto Rico: 1978

<i>ACP</i>			
<i>Causa de Muerte</i>	<i>Varones</i>	<i>Hembras</i>	<i>Razón (V ÷ H)</i>
<i>Accidentes</i>	26,057.0	6,167.0	4.2
<i>Cáncer</i>	12,898.5	11,397.0	1.1
<i>Enfs. del Corazón</i>	13,970.5	8,408.5	1.7
<i>Homicidios</i>	15,530.0	2,094.5	7.4
<i>Cirrosis Hepática</i>	7,972.5	1,717.5	4.6
<i>Suicidios</i>	7,350.0	1,512.5	4.9
<i>Neumonías</i>	3,553.5	3,235.0	1.1
<i>Enfs. Cerebrovasculares</i>	3,679.5	2,437.5	1.5
<i>Diabetes Mellitus</i>	1,402.5	1,907.5	0.7
<i>Arterioesclerosis</i>	482.0	265.0	1.8
<i>TOTAL -</i>	92,896.0	39,142.0	2.4

CUADRO 1: AÑOS DE CAPACIDAD POTENCIAL PERDIDOS ENTRE LAS EDADES DE 1 A 70 AÑOS
POR SEXO Y CAUSA PRINCIPAL
PUERTO RICO : 1978



necesariamente disminuye.

El desglose de ACP por sexo revela la medida en la cual la mortalidad prematura afecta predominantemente a los hombres. Mientras éstos constituyeron 58.7 por ciento del total de muertes registradas en el año 1978 (9), representaron más de un 70 por ciento de los años de capacidad productiva perdidos por las primeras diez causas de muerte. Con la excepción de la diabetes, la cual tiene un mayor impacto entre la población femenina, todas estas causas afectan principalmente a los hombres. El Cuadro I y la Tabla II ilustran las variaciones por sexo, destacándose las muertes violentas (homicidios, suicidios y acciden-

tes) y la cirrosis hepática como causas que tienen un impacto diferencial sobre los ACP entre la población masculina. Como se observa en la última columna de la Tabla II, la razón de ACP por sexo indica que el efecto de estas causas es de cuatro a siete veces mayor entre los varones que entre las hembras.

La Tabla III resume las diferencias en la importancia relativa de las primeras causas de muerte en términos de ACP. Es evidente que la mortalidad prematura varía notablemente entre un sexo y otro; los accidentes y los homicidios son las causas más importantes entre los varones, mientras el cáncer y las enfermedades del corazón lo son

TABLA III

Rango de Causas de Muerte en Términos de Años de Capacidad Potencial Productiva por Sexo
Puerto Rico: 1978

Causa de Muerte	Rango en ACP	
	Varones	Hembras
Accidentes	1	3
Homicidios	2	6
Enfermedades del Corazón	3	2
Cáncer	4	1
Cirrosis Hepática	5	8
Suicidios	6	9
Enfermedades Cerebrovasculares	7	5
Neumonías	8	4
Diabetes Mellitus	9	7
Arterioesclerosis	10	10

entre las mujeres.

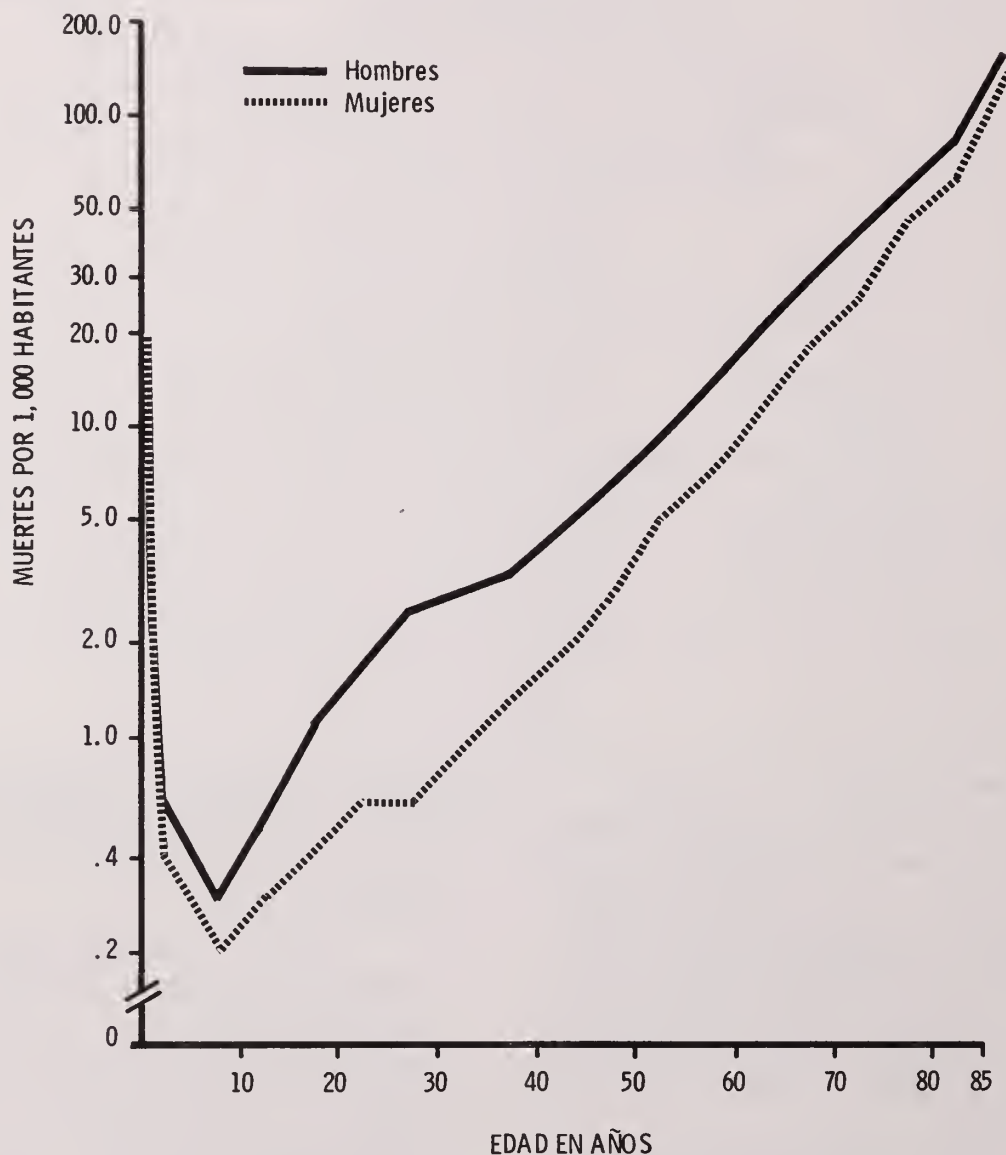
Estas diferencias se confirman cuando se comparan las tasas de mortalidad por grupo de edad y sexo. Como puede observarse en el Cuadro II, la población femenina tiene tasas más bajas en todos los grupos de edad. La diferencia entre los sexos se acentúa sobre todo entre las edades de 15 a 30, en las cuales la mortalidad masculina es casi tres veces mayor que la femenina.

Los varones manifiestan claramente un alza en la mortalidad en estas edades. Este fenómeno, denominado el *labor market entry hump*, ha sido atribuido a los abruptos cambios sociales que ha sufrido Puerto Rico en las últimas décadas (10). La emigración, la urbanización y la industrialización han creado presiones y tensiones entre este sector de la población puertorriqueña, situación que a su vez se manifiesta en un aumento en las muertes

violentas. Además, los varones jóvenes tienen las más altas tasas de desempleo (11), y la ociosidad involuntaria puede convertirse en una amenaza a la salud.

Un dato inquietante es que, a pesar de los logros alcanzados en reducir los riesgos de muerte en Puerto Rico, los varones jóvenes no parecen haberse beneficiado de las mejoras de salud que han afectado al resto de la población. De hecho, la probabilidad de morir *aumentó* para la población masculina entre 15 y 25 años de edad durante la década de 1960 a 1970. Esta tendencia se sostuvo para los de 25 a 35 años entre 1970 y 1975 (12), dato que sugiere que el cohorte nacido en la postguerra (1945-50), cuando la sociedad puertorriqueña comenzó a ser sacudida por los cambios asociados al crecimiento económico, ha resultado ser particularmente vulnerable a la muerte prematura.

CUADRO II: TASAS DE MORTALIDAD POR GRUPO. DE EDAD Y SEXO
PUERTO RICO : 1978



Discusión

Este intento por aplicar el índice ACP a la población de Puerto Rico no solo pondera las principales causas de muerte de acuerdo a

su impacto sobre la productividad, sino que también realza las diferencias en el impacto de una misma causa entre un sexo y otro.

Las diferencias en la mortalidad de los hombres y las mujeres han sido atribuidas a di-

ferencias biológicas; así concluyó una investigación epidemiológica realizada recientemente en los Estados Unidos (13). No obstante, los datos para Puerto Rico sugieren que la explicación no es tan fácil. El momento y el tipo de muerte varía tanto de un sexo a otro que las diferencias sugieren la intervención simultánea de factores ambientales y culturales: morimos en formas diferentes no sólo porque somos biológicamente diferentes, sino también porque vivimos de maneras diferentes y estamos expuestos a diferentes tipos de riesgo. Esto a su vez tiene implicaciones para las estrategias de salud.

Las muertes prematuras entre la población femenina no muestran gran vulnerabilidad. Estas se deben principalmente a causas de etiología compleja o desconocida (el cáncer, las enfermedades del corazón) en las cuales no es posible determinar o controlar todos los factores precursores a la condición.

La mortalidad masculina, sin embargo, parece ser más susceptible a reducción a través de estrategias preventivas. Más de la mitad de los años de capacidad productiva perdidos por las primeras diez causas de muertes son atribuibles a los accidentes, al homicidio y al suicidio. Estas tres causas son teóricamente evitables, por lo cual podrían reducirse. La magnitud de estas causas, junto con el impacto de la cirrosis hepática, señalan el efecto nocivo del comportamiento individual y colectivo del hombre puertorriqueño y las condiciones socio-económicas adversas a las cuales ha estado sujeto este sector de la población. Además, los hallazgos de estos cómputos apuntan hacia la relativa ineficacia de las intervenciones estrictamente médicas en la prolongación de la vida útil. Evaluadas en términos de su impacto en la capacidad productiva de la población, las principales causas de muerte de la población masculina tienen un alto contenido social. Así, la predominancia de las muertes violentas

nos obliga a ir más allá de los servicios de salud y aún del énfasis actual en los estilos de vida, para cuestionar nuestros valores como pueblo y nuestro funcionamiento como sociedad.

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SOBRE LAS INFLUENCIAS AMBIENTALES RELEVANTES A LA PREVENCION DEL DESARROLLO PRECOZ DE LA CATARATA SENIL

Manuel N. Miranda, MD y Sixto García Castiñeiras, MD, PhD

Resumen: Los autores presentan la hipótesis de que el factor geográfico detectable en la epidemiología de presbicie y catarata senil depende de efectos ambientales sobre la temperatura del cristalino. El efecto de la luz ultravioleta de la radiación solar parece ser de menos importancia en precipitar cambios senescentes en el cristalino.

Se ha llegado a esta conclusión por medio del análisis de datos epidemiológicos sobre el comienzo de la presbicie y prevalencia de la catarata senil en países con diferentes climas y en diferentes altitudes dentro del mismo país.

Desde el punto de vista preventivo, por tanto, parece ser más importante en climas cálidos evitar que la temperatura del cristalino suba que evitar que la luz ultravioleta de la radiación solar penetre en el ojo.

Summary: The hypothesis is presented that the geographical factor in the epidemiology of presbyopia and senile cataract is mediated through environmental effects upon the

temperature of the lens. Ultraviolet light effects of sunlight appear to be of lesser importance in accelerating the aging of the lens.

The hypothesis is based upon the analysis of epidemiological data on the onset of presbyopia and on the prevalence of senile cataract in countries with different climate and at different altitudes within the same country.

From the preventive aspect, therefore, it would seem more important in warm climates to try to decrease the rise in the temperature of the lens than to filter out the ultraviolet light component of sunlight reaching the eye.

Introducción

Tanto los cambios presbiópicos como los cambios que producen defectos en la transparencia del cristalino y eventualmente catarata senil probablemente representan la expresión de cambios naturales que ocurren con el envejecimiento en el cristalino y otros tejidos. En algunas personas, por influencias genéticas, dietéticas o ambientales, cuya importancia relativa no ha sido aún definida, tales cambios empezarían antes o se desarrollarían más deprisa. Hemos encontrado que un factor importante en precipitar el envejecimiento del cristalino parece ser la temperatura ambiental, según lo demuestra tanto un estudio

TABLA I

Comienzo de la Presbicie en Diferentes Regiones (*)

<i>Edad</i>	<i>Sitio</i>	<i>Latitud</i>	<i>Autor</i>	<i>Año</i>	<i>Temperatura °F (°C)</i>
47	INGLATERRA	51-54	AYRSHIRE	1964	51 (10.5)
43	INGLATERRA	51-54	TURNER	1958	51 (10.5)
45	NUEVA YORK	41-45	DUANE	1912	49 (9.4)
50	CLEVELAND	38-42	ALLEN	1961	50 (10.0)
45	JAPON	36-44	KAJIURA	1965	58 (14.4)
43	JAPON	36-44	FUKUDA	1965	58 (14.4)
42	JAPON	36-44	ISHIHARA	1919	58 (14.4)
43	CALIFORNIA	32-42	HAMASAKI	1956	60 (15.5)
41	ISRAEL	32	RAPHAEL	1961	63 (17.2)
40	SUDAFRICA	26-29	COATES	1965	63 (17.2)
37	INDIA	10-30	RAMBO	1960	79 (26.1)
39	PUERTO RICO	18-18.5	MIRANDA	1977	79 (26.1)

(*) Datos tomados de referencia 1.

que uno de los autores (1) realizó sobre el comienzo de la presbicie como el análisis de la literatura oftalmológica sobre la prevalencia de catarata senil.

Materiales y Métodos

El propósito de este trabajo fue el de determinar las edades de comienzo de presbicie y cataratas seniles en pacientes de otros países y comparar ésta con las edades en pacientes en Puerto Rico. De igual forma se trató de correlacionar estas edades con las temperaturas prevalecientes en los diferentes países y con diferentes altitudes dentro del mismo país.

El procedimiento utilizado para determinar la amplitud de acomodación en pacientes puertorriqueños ha sido discutido en detalle previamente (1). Hemos tomado como criterio de presbicie una am-

plitud de acomodación reducida a 3.50 D como mínimo.

Las edades de comienzo de presbicie en pacientes de otros países se obtuvieron mediante un cuestionario enviado a 1,500 oftalmólogos de todo el mundo (1).

La literatura referente a catarata senil se obtuvo mediante la búsqueda personal y experiencia acumulada de los autores y a través de búsquedas computerizadas disponibles (MED-LINE, Biblioteca, Recinto de Ciencias Médicas).

Resultados

Presbiopía

En Puerto Rico la edad promedio de desarrollo de presbiopía está entre los 38 y 39 años.

TABLA II

Correlación entre la Temperatura Anual y la Edad
Promedio del Comienzo de la Presbicie en Ambos Sexos (*)

<i>País</i>	<i>Temp.</i> <i>°F(°C)</i>	<i>Edad</i>	<i>País</i>	<i>Temp.</i> <i>°F(°C)</i>	<i>Edad</i>
NORUEGA	42 (5.5)	46.1	ARGENTINA	61 (16.1)	43.6
FINLANDIA	42 (5.5)	44.5	URUGUAY	61 (16.1)	45.5
ALASKA	42 (5.5)	44.1	SUDAFRICA	63 (17.2)	41.5
CANADA	42 (5.5)	44.7	AUSTRALIA	63 (17.2)	44.8
SUECIA	43 (6.1)	43.8	GRECIA	64 (17.7)	42.9
DINAMARCA	46 (7.7)	42.5	EE. UU.. SUR	65 (18.3)	42.9
EE. UU. NORTE	46 (7.7)	44.0	PERU	68 (20.0)	42.4
ALEMANIA	48 (8.8)	43.5	GUATEMALA	69 (20.5)	39.6
IRLANDA	48 (8.8)	46.5	COSTA RICA	69 (20.5)	40.8
HOLANDA	49 (9.4)	45.3	BRASIL	69 (20.5)	42.3
BELGICA	49 (9.4)	44.8	BOLIVIA	73 (22.7)	40.5
AUSTRIA	49 (9.4)	44.5	EGIPTO	73 (22.7)	39.5
INGLATERRA	51 (10.5)	45.3	EL SALVADOR	75 (23.8)	40.5
FRANCIA	51 (10.5)	45.5	HAWAII	75 (23.8)	42.4
EE. UU. MEDIO	51 (10.5)	43.3	VENEZUELA	76 (24.4)	39.8
HUNGRIA	52 (11.1)	41.5	ECUADOR	78 (25.5)	39.7
BOLIVIA (M)	52 (11.1)	44.5	INDIA	79 (26.1)	40.0
PERU (M)	55 (12.7)	44.5	COLOMBIA	79 (26.1)	39.8
ECUADOR (M)	55 (12.7)	42.5	REP. DOMINICANA	79 (26.1)	39.5
ESPAÑA	56 (13.3)	44.5	HAITI	79 (26.1)	38.5
TURQUIA	58 (14.4)	44.5	PUERTO RICO	79 (26.1)	39.8
COLOMBIA (M)	58 (14.4)	42.5	FILIPINAS	79 (26.1)	37.8
CHILE	59 (15)	44.8	INDONESIA	80 (26.6)	38.5
ITALIA	60 (15.5)	44.5	PANAMA	80 (26.6)	40.8
IRAN	61 (16.1)	43.5	MALASIA	81 (27.2)	38.9
MEXICO	61 (16.1)	43.3	NICARAGUA	83 (28.3)	39.8
			TAILANDIA	83 (28.3)	40.5

(M) = MONTAÑAS

(C) = COSTAS

(T) = TROPICAL

(*) Datos tomados de referencia 1.

TABLA III

Prevalencia de Cataratas como Porcentaje de Causas de Ceguera (*)

<i>País</i>	<i>Latitud</i>	<i>Temperatura °F (°C)</i>	<i>Prevalencia Porcentaje</i>
ARTICO CANADIENSE	N 65-75	17 (-8.3)	3.6
CANADA	N 42-55	42 (5.5)	18.0
INGLATERRA	N 51-54	51 (10.5)	22.0
ESTADOS UNIDOS	N 25-49	54 (12.2)	20.0
COREA	N 35-41	66 (18.8)	36.0
TAILANDIA	N 13-20	83 (28.3)	40.0
PUERTO RICO	N 18-18.5	79 (26.1)	46.0
INDIA	N 9-27	79 (26.1)	40.0
NIGERIA	N 6-12	80 (26.6)	35.0
KENIA	N 5-S 5	77 (25.0)	43.6

(*) Datos tomados de referencia 11.

La Tabla I compara los resultados obtenidos en Puerto Rico con otros publicados en diferentes países. Nótese la relación negativa entre el promedio anual de temperatura y la edad promedio de comienzo de la presbicie. Esta relación se demuestra con mayor claridad en la figura 1, construida con los datos de la Tabla I. Cuanto mayor es la temperatura promedio anual antes comienza la presbicie.

La Tabla II recoge la información obtenida de las contestaciones al cuestionario mencionado antes. En la figura 2 se representan gráficamente los datos de la Tabla II. De nuevo se pone de relieve el comienzo tardío de la presbicie en las regiones frías y su comienzo temprano en las regiones cálidas.

Catarata Senil

La literatura oftalmológica ofrece una

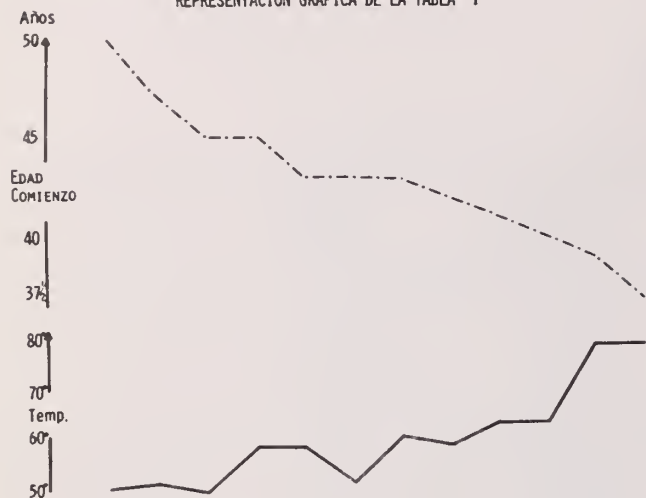
multitud de datos, todos respaldando la suposición de que la catarata senil, al igual que la presbicie, se desarrolla más temprano y es más común en regiones con temperatura promedio anual elevada.

La Tabla III muestra la prevalencia de las cataratas como por ciento de causa de ceguera en diferentes países. La representación de la Tabla III en la figura 3 demuestra que la prevalencia de cataratas es mayor en aquellos países con temperaturas anuales más altas.

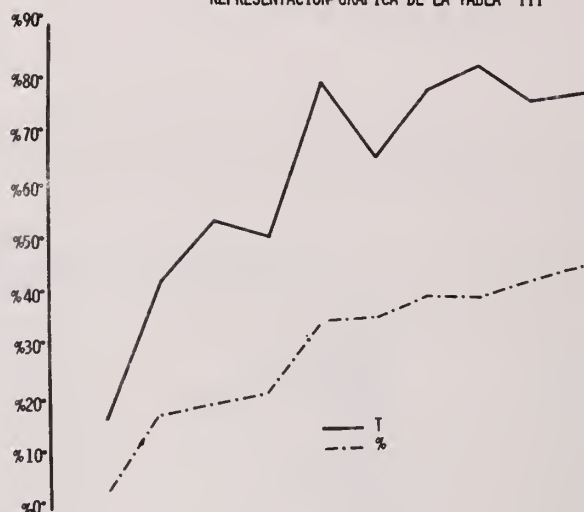
Caird (2) comparó el riesgo de extracción de catarata que existe en Israel y en Oxford. Tal riesgo es mucho mayor en Israel que en Inglaterra según se puede apreciar en la Tabla IV. La temperatura promedio en Israel es de 63°F (17.2°C) mientras que en Inglaterra es de solamente 51°F (10.5°C).

Van Heyningen (3) estudió y comparó las cataratas removidas en 1969 y 1970

REPRESENTACION GRAFICA DE LA TABLA I



REPRESENTACION GRAFICA DE LA TABLA III



REPRESENTACION GRAFICA DE LA TABLA II



al 1968 los ojos de 29,688 personas, casi toda la población, que vivían en las planicies y montañas de Punjab (India). La Tabla V muestra el porcentaje de prevalencia de catarata y afaquia por edad. En las planicies, donde el promedio de la temperatura anual es más alta que en las montañas, la prevalencia de cataratas y de afaquia fue significativamente mayor.

El Dr. R. P. Pokhrel, Director del Departamento de Oftalmología del Hospital de Ojos de Nepal y del Hospital Bir, en comunicación personal al Dr. R. H. Meaders de la Fundación Internacional de los Ojos (National Eye Foundation) escribe:

“Nosotros tenemos un número limitado de cirujanos oftálmicos para hacer frente a los problemas oftalmológicos del país. Así que organizamos de 15 a 20 campamentos móviles de oftalmología al año durante el invierno (de octubre a marzo) y operamos aproximadamente de 6,000 a 8,000 cataratas por año. Los expedientes de nuestros campamentos son fascinantes porque demuestran que a altitudes

en Oxford (Inglaterra) y Shikarpur (Pakistan). Ella encontró que en Shikarpur las cataratas son mucho más frecuentes, aparecen a una edad más temprana y se desarrollan más rápidamente que en Oxford. La temperatura promedio anual en Pakistan es de 78°F (25.5°C) mientras que la de Inglaterra es de solamente 51°F (10.5°C).

Un grupo de oftalmólogos encabezados por Chatterjee (4) examinaron del 1966

TABLA IV

Riesgo de Extracción de Catarata en Israel y Oxford

(Cataratas extraídas por cada 10,000 operaciones por año) (*)
(Hombres)

Edad (Años)	ISRAEL		Oxford
	De origen europeo	De origen oriental	
40-49	1.42	3.76	0.3
50-59	4.50	15.75	2.3
60-69	16.68	37.73	6.4
70 +	40.36	63.30	19.7

Caird et al, 1965 (Oxford)

Halevi y Landau, 1962 (Israel)

(*) Datos tomados de referencia 2.

TABLA V

Prevalencia de Cataratas y Afaquia por Edades (*)

Edad (Años)	Planicies	Montañas **
30-39	2.6	0.0
40-49	9.0	0.8
50-59	22.5	12.8
60 +	31.4	17.6

* Tomado de referencia 4.

** De 1,219 m (4,000 pies) a 4,572 m (15,000 pies)

menores de 4,000 pies (1,200 m), es común encontrar cataratas maduras a la edad de 40 años y aún a los 35; en las montañas de 4,000 a 7,000 pies (2,100 m) de altura, el promedio de edad del desarrollo de la catarata es de 60 años; y en alturas mayores, sobre 7,000 pies, no suelen encontrarse cataratas antes de los

70 o 75 años".

Hiller et al (5) en uno de los más sólidos y recientes trabajos epidemiológicos sobre catarata encuentra que existe una mayor prevalencia de cataratas en personas de más de 64 años de edad en regiones geográficas de USA que reciben anualmente más

horas de luz solar. Es una lástima que estos autores no hayan recogido los promedios de temperatura en las regiones geográficas incluidas en el estudio.

Zigman (6) encuentra que la incidencia de cataratas oscuras y brunescentes aumenta a medida que uno se acerca al ecuador. Y reporta también que son más abundantes este tipo de cataratas en ocupaciones al aire libre que en ocupaciones de ambientes cerrados. Estos resultados los interpreta Zigman como debidos a la cantidad de luz ultravioleta solar que recibe el ojo, que es mayor en los trópicos y en ocupaciones al aire libre. Aunque no hay duda de que la cantidad de luz ultravioleta que recibe la tierra aumenta hacia el ecuador, también aumenta en la misma dirección la temperatura promedio anual; razón por la cual no se justifica sostener que el factor decisivo en la epidemiología de la catarata senil es el contenido en luz ultravioleta de la radiación solar.

Discusión

Tanto la presbicia como la catarata senil son patologías relacionadas con el envejecimiento del lente cristalino. La relación que existe entre ambos procesos no se ha establecido, pero podemos asumir que aquello que acelere epidemiológicamente el desarrollo de la presbicia hará lo mismo en el caso de la catarata senil.

La temperatura del interior del ojo no es uniforme. Esto se debe a que gran parte del volumen del ojo es avascular. Las zonas intraoculares cuya temperatura se acerca más a la temperatura central corporal deben ser las más próximas a las capas vasculares del ojo. La forma esférica del ojo posiblemente contribuya a que la región central de la esfera reciba el calor de la capa coroidea de una ma-

nera relativamente efectiva. Sin embargo, el polo anterior del ojo está sometido a la influencia de la temperatura ambiental. En temperaturas ambientales menores que la corporal, la temperatura corneal debe ser más baja que la del resto de las estructuras oculares.

Se han hecho estudios detallados de temperatura intraocular en el conejo (7), a lo largo del eje anteroposterior que demuestran, en efecto, que la temperatura aumenta anteroposteriormente, siendo la de la córnea varios grados más baja que la central. Estos estudios también indican que la temperatura de los tejidos oculares baja a medida que la temperatura ambiental se disminuye desde 27°C hasta 2-3°C. La caída más grande ocurre en el cristalino, lo cual sugiere una sensibilidad especial de esta estructura a cambios en la temperatura ambiental. La forma de la curva de descenso de la temperatura en los diferentes tejidos oculares (menos la córnea) es exponencial, lo que sugiere una relación compleja entre las temperaturas ambiental, central y ocular.

Un factor adicional a tenerse en cuenta al considerar la temperatura de los tejidos intraoculares es la transparencia de los mismos, necesaria para la visión, pero que permite que radiación visible y no-visible penetre y sea absorbida en diferentes grados por las estructuras oculares (8). Luz visible de 400 a 700nm es la que llega con preferencia a la retina. Luz ultravioleta desde 293nm hasta cerca de 400nm es absorbida por el cristalino ya que no es absorbida totalmente por la córnea. Desde el punto de vista fotoquímico estas longitudes de onda serían las más perjudiciales para el cristalino. Varias bandas por encima de 700nm penetran la córnea y pueden ser absorbidas por estructuras oculares posteriores. Desde el punto de vista de aumento en la temperatura intraocular, longitudes de onda próximas y por encima de 700 nm (infrarojas) son las

más efectivas.

Se ha insistido en el papel nocivo de la luz ultravioleta que llega al cristalino (6). Alteraciones químicas desencadenadas en las proteínas del cristalino por esta luz serían responsables de los cambios relacionados con el envejecimiento del mismo y con el desarrollo de la catarata senil. Sin embargo, los datos presentados sobre el desarrollo de las presbicie y sobre la prevalencia de catarata senil no son explicables sobre esta base. Es sabido que dentro de la misma región geográfica áreas montañosas altas reciben mayor radiación ultravioleta que áreas bajas próximas al nivel del mar (10). Datos sobre la edad de aparición de presbicie en países como Colombia, Bolivia, Ecuador y Perú (Tabla II, figura 2) que tienen tanto zonas montañosas como zonas bajas, indican que la presbicie se desarrolla antes en las áreas bajas donde la cantidad de luz ultravioleta es más pequeña pero donde la temperatura promedio anual es más elevada que en las montañas.

Lo mismo puede decirse en cuanto a la prevalencia de catarata senil en la India.

Nos parece improbable que la relación epidemiológica encontrada en diferentes países entre temperatura y parámetros clínicos de envejecimiento del cristalino dependa consistentemente de otros factores, tal y como factores genéticos o dietéticos, para indicar los más mencionados. Sin embargo, estudios epidemiológicos adicionales en los que se disminuyan al máximo las posibilidades de distorsión involuntaria de los datos por factores no climáticos, son aún necesarios para establecer sobre base indiscutible la influencia de la temperatura sobre el envejecimiento del cristalino.

Dos mecanismos básicos podrían explicar la correlación epidemiológica entre temperatura ambiental y presbicie o catarata senil:

1. Una temperatura ambiental elevada sostenida disminuiría el gradiente de temperatura que normalmente existe antero-posteriormente en el ojo y aumentaría especialmente la temperatura del cristalino, debido a la sensibilidad de esta estructura a los cambios ambientales de temperatura.

2. La radiación solar que llega al ojo produciría, de ser absorbida por el cristalino, un aumento local en su temperatura. Esta radiación estaría en relación directa con el número de horas de exposición al sol de una región y con el ángulo con que la luz solar incide sobre la superficie. Hiller et al (5) han demostrado que la incidencia de catarata senil depende del número de horas de exposición solar de una región.

Como consecuencia de estos dos mecanismos el cristalino estaría expuesto en climas cálidos a temperaturas más elevadas que en climas fríos.

La exposición del cristalino a temperaturas altas puede tener consecuencias directas sobre su actividad metabólica y sobre la actividad de sus sistemas de transporte de sustancias. Hay que señalar que no es necesaria la denaturación térmica de las proteínas del cristalino para que ocurran cambios apreciables en su metabolismo y en la fluidez de sus membranas celulares.

La mayoría de las células vivientes llevan a cabo sus actividades biológicas entre los 10° y 45°C (8). La velocidad con que ocurren estas reacciones depende grandemente de la temperatura actual dentro de esos límites. Aunque no es posible por ahora definir concretamente la magnitud de estos efectos en el cristalino, es posible predecir que un aumento sostenido, por pequeño que sea, en la temperatura a que desarrolla sus funciones puede tener consecuencias importantes a largo

plazo. Es probable que un metabolismo lenticular acelerado durante años y alteraciones en la cinética del transporte lenticular de sustancias, conduzcan a una situación en que las alteraciones seniles se desarrolle fácilmente en el cristalino.

¿Sería posible prevenir un aumento sostenido en la temperatura del cristalino en climas cálidos?

Sobre la base del posible efecto fotoquímico nocivo de la luz ultravioleta se ha recomendado el uso de espejuelos que absorban esta radiación (6). Aunque esta hipótesis no parece válida según hemos indicado anteriormente, el uso de espejuelos capaces de disminuir la entrada al ojo de radiaciones con efecto térmico sí creemos que es recomendable. En este sentido cristales teñidos que absorban radiación de longitud de onda próxima y por encima de 700nm serían especialmente útiles de acuerdo a nuestra hipótesis. No sabemos aún si este tipo de protección es efectiva para eliminar a la larga el efecto de la temperatura ambiental sobre los gradientes oculares de temperatura (mecanismo 1), pero por lo menos debe ser efectiva en reducir el calentamiento directo del cristalino por radiación absorbida (mecanismo 2). En este momento estamos diseñando y realizando experimentos en animales para someter a prueba estas posibilidades, que serán objeto de un próximo reporte.

Agradecimiento

Los autores agradecen profundamente la valiosa

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También queremos expresar su agradecimiento a la Sra. Carmín C. de Cabra y la Sra. Teresita Ramos Berrios por su excelente trabajo secretarial en la elaboración del manuscrito.

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STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Miguel Vázquez Botet, MD and Jorge L. Sánchez, MD

Report of a Case

A 14-month-old boy had a two-day history of tenderness in the axillae, fever and dermatitis consisting of large flaccid blisters and exfoliation on the neck, face and trunk and some lesions on the extremities. The patient had been given acetaminophen and a mixture of chlorpheniramine maleate and phenylephrine for his dermatitis and fever and had received no medications previously. Past medical history was unremarkable.

On examination, the patient's vital signs were normal. The abnormal physical findings were limited to the skin, nasal mucosae and lymph nodes. There was diffuse erythema, with oozing and crusting on the nares, face, groin, and perineal region, as well as multiple erosions on the face, upper portion of the trunk and the lower extremities (Fig. 1). There was also generalized erythema. The Nikolski sign (dislodging of the epidermis with lateral finger pressure) was present on erythematous skin sites. There was anterior and posterior cervical adenopathy.



Fig. 1: Erythema of the right lower extremity with moist exfoliated patches on areas where flaccid bullae were present.

1. The most likely clinical diagnosis is:

- a. Scarlet Fever
- b. Atopic Dermatitis
- c. Erythema Multiforme

- d. Staphylococcal Scalded Skin Syndrome
- e. Toxic Epidermal Necrolysis-Adult Type

2. Rapid diagnostic methods so that appropriate therapy can be quickly instituted include:

- a. Skin scraping for fungi
- b. ASO titer
- c. Exfoliative cytology of skin lesions
- d. Frozen sections of skin specimens
- e. Complete blood count

Frozen sections of bullous skin lesions showed intraepidermal separation within the stratum granulosum. *Staphylococcus Aureus* organisms grew from cultures from the external nares and conjunctivae. Skin, throat, urine and blood cultures were negative. The CBC was within normal limits. The WBC count was 10,900/ cu mm, with 55 percent polymorphonuclear leukocytes, 4 percent band cells, 15 percent lymphocytes, 1 percent plasma cells, 23 percent monocytes and 2 percent eosinophils. Results of urinalysis, SMA₁₂, ASO titer and chest X-rays were normal.

A biopsy specimen from the erythematous skin on the lateral portion of the chest in which the Nikolski sign was present showed epidermal cleavage with splitting within the stratum granulosum (Figs. 2 and 3). There was minimal inflammatory infiltrate in the upper portion of the dermis.

3. The treatment of choice for *Staphylococcal Scalded Skin Syndrome* (SSSS) is:

- a. Lincomycin
- b. Penicillin
- c. Cephalosporins
- d. Erythromycin
- e. Semisynthetic, penicillinase-resistant penicillins

4. The mortality of SSSS in the antibiotic era is close to:

- a. 5 percent
- b. 20 percent
- c. 50 percent
- d. 70 percent
- e. 90 percent

The patient received intravenous methicillin therapy for 4 days followed by oxacillin sodium orally, and was treated topically with an ointment that contained bacitracin. His re-



Fig. 2: Epidermal cleavage with splitting within the stratum granulosum. The remainder of the epidermis appears unremarkable and the dermis contains a slight superficial perivascular mononuclear cell infiltrate. (Hematoxylin and eosin stain, original magnification x10).

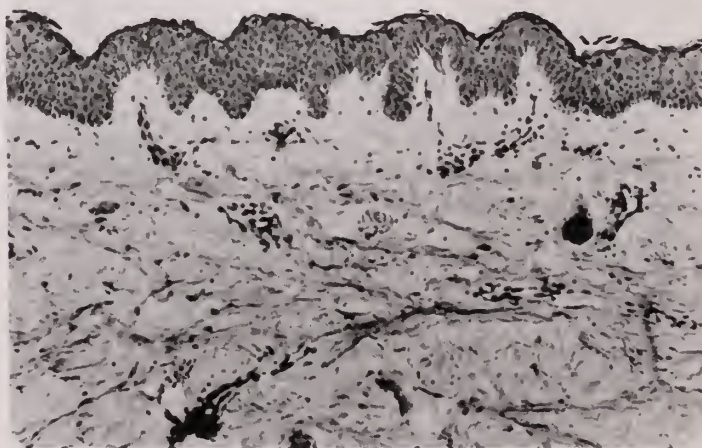


Fig. 3: See legend for Fig. 2 (Hematoxylin and eosin stain, original magnification x 100).

covery was rapid and complete.

Comments

Toxic epidermal necrolysis (TEN) is

an extremely severe bullous eruption seen in all age groups. It is clinically manifested by exquisitely tender, intensely erythematous skin, superficial fine vesicles and bullae supervene; large sheets of epidermis are then shed, leaving erosive red areas. It has been divided into two categories that differ on the basis of histological findings, patient-age predilection and etiologic factors.

One of these forms occurs chiefly in adults (Adult TEN) and carries a high mortality rate up to 50 percent from attendant fluid, electrolyte, and colloid loss because the entire epidermis is destroyed and detaches from underlying dermis. In this variety, drugs are the most frequently implicated etiologic factor but it also has been associated to lymphomas, vaccinations, measles, carbon monoxide poisoning, radiotherapy, and graft-versus-host reactions. The administration of systemic corticosteroids is indicated and questionably reduces the mortality. The prognosis in drug-induced TEN is guarded.

The other form, termed the Staphylococcal Scalded Skin Syndrome (SSSS), primarily afflicts children under the age of 5 years. The etiology of this syndrome is linked to the elaboration of a distinctive exotoxin (epidermolysin) produced by phage group II strains of *Staphylococcus Aureus*, mostly phage type 71, which preferentially attack the epidermis of susceptible species at the subgranular level. Fortunately, rapid recovery is the rule, regardless of the initial drug that is chosen. However, the disease still carries a significant mortality (3 to 4 percent) and the morbidity from occasional patients who develop cellulitis, sepsis and pneumonia should not be ignored. Antibiotic therapy with a penicillinase resistant penicillin is the treatment of choice. While some authors claim that the disease is not influenced by ther-

apy with corticosteroids, others have concluded that systemic corticosteroids may in fact, aggravate the clinical picture.

Since the prognosis and morbidity may be affected by the initial choice of therapy and the diagnosis can not be based on age alone, the clinician needs rapid diagnostic methods so that appropriate therapy can be quickly instituted. Two such methods are available. Frozen sections of skin and exfoliative cytology will aid in the differentiation of the two variants. Granular layer or upper-stratum-malpighian cleavage of the epidermis is characteristic of the staphylococcal induced variant, in contrast to full-thickness or suprabasal cleavage associated with other causes (adult TEN). Exfoliative cytology of skin lesions will show acantholytic keratinocytes in SSSS or inflammatory cells and necrotic keratinocytes in adult TEN. Of the two techniques, frozen sections to determine the site of cleavage in the epidermis is probably the one which requires less training and experience in the interpretation of the test.

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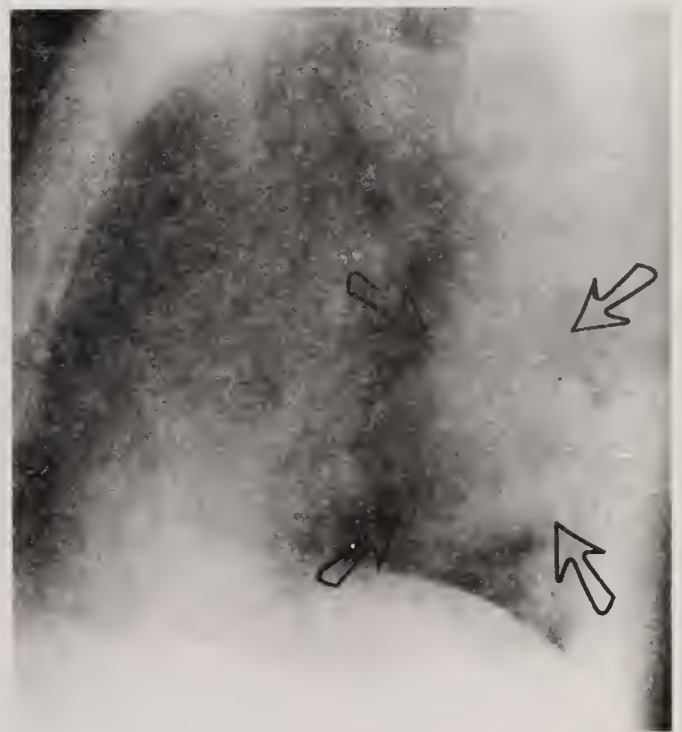
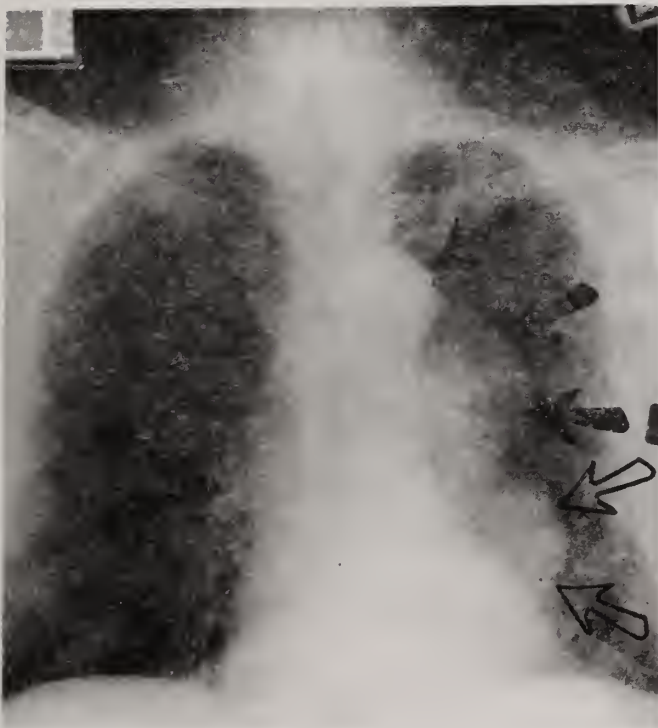
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Dermatology Department
University of Puerto Rico
School of Medicine

(Contestaciones en página 35)

José Couto, MD, Ildefonso Rivera, MD y Osvaldo Jiménez, MD
Cardiology Service, Veterans Administration Hospital

Paciente varón de 67 años de edad, se presenta a la sala de emergencia con dolor precordial opresivo y fatiga. En el 1971 fue operado debido a un aneurisma de la aorta descendente. Las figuras 1 y 2 demuestran la placa de pecho tomada en la sala de emergencia.



El diagnóstico más probable es:

1. *Quiste pericárdico.*
2. *Tumor de pericardio.*
3. *Aneurisma ventricular.*
4. *Aneurisma aórtico.*
5. *Tumor pulmonar.*

CONTESTACION



4. Aneurisma aórtico.

La figura 1 demuestra una silueta cardíaca de tamaño normal y un arco aórtico y aorta descendente calcificadas y tortuosas (flechas negras). La placa es sugestiva de un aneurisma de la aorta descendente (flechas blancas). La figura 2 demuestra que la anomalía ilustrada en la figura 1, se origina en la aorta descendente. La figura 3 ilustra el aortograma en la posición obliqua anterior izquierda. La flecha negra indica la tortuosidad previamente señalada en la figura 1, las flechas blancas señalan el aneurisma de la aorta descendente.

New evidence is in: Treatment of mild hypertension can save lives

Even among patients with DBP in the low 90s, systematic therapy significantly reduced mortality:

- Of nearly 11,000 hypertensives identified by the Hypertension Detection and Follow-up Program, slightly more than 70% had mild hypertension (DBP 90-104 mm. Hg).¹
- Half were given systematic and aggressive care in HDFP centers; half were referred to customary sources of medical care.
- After 5 years, HDFP found that effective treatment of mild hypertension may reduce premature deaths by 20%.¹
- As part of HDFP's systematic treatment and follow-up program, the primary step-1 agent was chlorthalidone: Hygroton.^{®2}

**The primary agent used by the HDFP
in an effective low dose**

Hygroton[®] 25 mg.
(chlorthalidone USP)
one a day

**Because there's nothing mild
about mild hypertension**

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance, namely hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and

related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aquea) in bottles of 100, 1000 and 5000, 25 mg. (peach) in bottles of 100 and 1000, unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

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LABORATORIES

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Fragile



handle with **HALDOL**[®] (haloperidol) tablets/concentrate/injection

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HALDOL haloperidol effectively controls psychotic symptoms, including disruptive behavior, without undue sedation—permitting a better quality of life for many disturbed elderly patients.¹ While some instances of drowsiness have been reported, marked sedation is rare.

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HALDOL is unlikely to cause hypotension which can result in dizziness and falls.² Transient hypotension seldom occurs; severe orthostatic hypotension has not been reported.

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Blurred vision, dry mouth, constipation and urinary retention—which can be extremely upsetting to older

persons suffering from dementia—are infrequent with HALDOL.³

Extrapyramidal symptoms, when seen, are generally dose-related and readily controllable; usually they do not occur at the very low doses of HALDOL used in treating the elderly.^{4*}

Tasteless, odorless, colorless concentrate

HALDOL concentrate can be added to food, juices or water to improve acceptability in patients unwilling or unable to swallow solid medication. It also permits the very small dosage adjustments sometimes needed for geriatric patients.

*Persistent extrapyramidal symptoms may require discontinuation of the use of the drug.

Photograph posed by professional model

Please turn page for summary of prescribing information.



concentrate

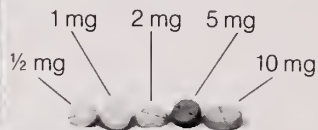
A tasteless, odorless, colorless liquid concentrate for better patient acceptability. 2 mg per ml haloperidol (as the lactate).

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A rapid-acting injection for psychiatric emergencies. 5 mg haloperidol (as the lactate) with 1.8 mg methylparaben and 0.2 mg propylparaben per ml, and lactic acid for pH adjustment to 3.4 ± 0.2 .

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5 tablet strengths for convenience in individualizing dosage:



HALDOL® (haloperidol)

tablets/concentrate/injection

A dosage form for every therapeutic need

Summary of Prescribing Information

Contraindications: Severe, toxic CNS depression or comatose states from any cause, hypersensitivity to the drug, Parkinson's disease.

Warnings: Usage in Pregnancy: Safe use in pregnancy or in women likely to become pregnant has not been established, use only if benefit clearly justifies potential hazards. Infants should not be nursed during drug treatment.

Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity.

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticonvulsant medication since HALDOL haloperidol may lower the convulsive threshold; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants. Concomitant antiparkinson medication, if required, may have to be continued after HALDOL haloperidol is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time. The 1, 5, 10 mg tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Adverse Reactions: CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyra-

midal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn.

Persistent Tardive Dyskinesia: Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by reinstitution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms.

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice reported. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia and hypoglycemia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration.

The injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

Caution: Federal law prohibits dispensing without prescription.

08628

IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

HALDOL tablets and concentrate (120 ml) are manufactured by McNeil Pharmaceutical Co., Dorado, PR 00646.

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**DISCURSO PRONUNCIADO POR EL DR. ANTONIO DE THOMAS
AL TOMAR POSESION COMO PRESIDENTE DE LA ASOCIACION
MEDICA DE PUERTO RICO EL 29 DE NOVIEMBRE DE 1980**

Constituye un alto honor y un gran privilegio el dirigirme a ustedes, mis compañeros médicos y distinguidos invitados, como Presidente de esta noble y prestigiosa Institución, que por los últimos 78 años se ha dedicado a proteger la salud del pueblo puertorriqueño y a defender a todos los médicos puertorriqueños.

Quiero expresar mi más profundo agradecimiento a mis compañeros de profesión, que a lo largo de varios años me han ofrecido su respaldo y su aliento en las diferentes posiciones que he ocupado en nuestra Asociación.

Me permito hacer un reconocimiento especial a mi querida esposa, María Isabel, y a mis adorados hijos, Antonio y María Mercedes, por su continuo sacrificio ante las responsabilidades en que he estado envuelto. Quiero agradecer a mis queridos padres, que no me pueden acompañar en el día de hoy, pero que sus esfuerzos y sacrificios han hecho posible que yo pueda estar aquí en este día, y quienes estoy seguro en estos momentos comparten conmigo el júbilo de la ocasión.

Teóricamente yo soy hijo único y no tengo hermanos, dije teóricamente porque en la realidad Dios me ha brindado la bendición de haberme unido a esa prestigiosa familia Cabrera de la Rosa, donde he encontrado muchos hermanos que me han ofrecido su cariño, su amor y su ayuda por siempre. Rindo homenaje a todos ellos, queridos hermanos.

No pretendo en estos momentos cansarles con un alarde de oratoria, pletórica de frases agradables al oído, pero que como palabras al fin, se las lleva el viento y solo quedan de ellas vanos recuerdos resultantes de la interpretación que sobre las mismas puedan hacer el que las ha oído. Sí permítanme expresar algunas ideas y conceptos que como profesional me preocupan y han estado preocupando siempre.

Constituye el ejercicio de la profesión médica un sacerdocio que como tal, todos nosotros abrazamos cuando decidimos en un momento dado estudiar medicina. Al así decidirlo estábamos, como ahora lo estamos, conscientes de las responsabilidades y sacrificios que conlleva el ejercicio de nuestra profesión. Si aceptamos estas responsabilidades y sacrificios y si se nos exige en el ejercicio de nuestra profesión el descargo de éstas, nosotros, por derecho inherente a los mismos, reclamamos ser la voz decisiva en todo aquello que concierna al ejercicio de la profesión y a la salud. Tristemente, hemos pasado por la experiencia de que personas carentes de los más mínimos conceptos referentes al ejercicio de nuestra profesión y a los problemas de salud que aquejan a nuestros conciudadanos han establecido pautas completamente erróneas con resultados adversos y perjudiciales para los pacientes.

Si triste y lamentable es que personas carentes de conocimiento médico establezcan pautas médicas, más triste y lamentable es que, como ha sucedido, algunos miem-

bros de nuestra profesión pretendan poseer un patrimonio exclusivo sobre el conocimiento y la sapiencia médica. El conocimiento y la sapiencia médica no pertenece a ningún médico en particular con exclusión de los demás sino que pertenece a todos y cada uno en general. Hemos pasado por la triste experiencia durante el transcurso de los últimos veinte años de ver cómo legislación importante que afecta la salud y a nuestra profesión se ha establecido sin el concurso de los médicos y en muchas ocasiones en contra de nuestras recomendaciones.

Diariamente vemos personas que expresan conceptos equivocados y críticas injustificadas de nuestra profesión y de nuestros médicos, creando ante la opinión pública una imagen errónea y prejuiciada. Igualmente, vemos personas que en un momento de desesperación recurren al médico para que éste, atienda y recupere su salud, bien sea de ellas o de un ser querido, pero al momento de pagar sus honorarios, no importa lo razonables que estos sean, expresan insatisfacción y críticas. Mas, estas mismas personas no reaccionan de igual forma cuando pagan por obtener un divorcio o por obtener una licencia de portar armas o por jugar un cuadro en el hipódromo. Los médicos, al igual que todos los otros profesionales, buscamos el diario vivir de nuestras familias, ejerciendo nuestra profesión. No nos quejamos del sacrificio que el ejercicio de la misma conlleva, pero lo que no podemos permitir son las críticas mal intencionadas y las injusticias deliberadas contra nuestra profesión. Ante estas mezquindades, toda la clase médica, todos los Médicos Puertorriqueños debemos pararnos y con decisión de carácter, decirles "Basta Ya".

Quiero en estos momentos dejar claramente establecido que en algunas ocasiones ha habido y habrán críticas constructivas. Estas las debemos analizar con el más estricto sen-

tido de responsabilidad para obtener de las mismas el mayor beneficio que nos conduzca a la superación profesional.

En diferentes ocasiones, durante el transcurso de los años que he sido miembro de esta Asociación, se me ha dicho, tanto por compañeros médicos como por personas no-médicos, que la Asociación Médica de Puerto Rico constituye una élite de médicos. A estas personas les he dicho que no hay nada más lejos de la verdad que estas expresiones. Médicos, les digo que nuestra Asociación Médica de Puerto Rico está siempre abierta para todos los médicos. Debemos estar conscientes de que, en adición a los miembros de esta históricamente honorable Asociación, hay fuera de la misma compañeros médicos tan dedicados y prestigiosos como cualesquiera de nosotros.

Constituyen estas palabras una voz de alerta a los compañeros, y al decir compañeros, me refiero a todos los Médicos Puertorriqueños. Considero necesario e imprescindible el que todos nos unamos, para que, manos con manos, hombros con hombros, obtengamos la realización de nuestros propósitos, que no tan solo son el defender la profesión médica de los ataques e injustas críticas, sino que también con la más profunda inteligencia que el hombre pueda desarrollar, podamos cumplir con nuestra misión que es el ejercicio de la medicina para el bienestar del paciente.

No quiero terminar mis palabras sin antes expresar al Honorable Médico Puertorriqueño, Dr. Ramón M. Suárez, mis más altos respetos y, a él, junto con todos los otros médicos que como él nos han precedido y que con la nobleza de corazón y fortaleza de espíritu supieron trillar el camino que hasta aquí nos ha conducido, mi humilde, pero sincero agradecimiento.

No he querido en el día de hoy ex-

presar qué haré o no haré durante mi Presidencia, puesto que prefiero la acción a las palabras, ya que al culminar mi gestión serán ustedes, mis queridos compañeros, los jueces de mis actos.

Ofrezco en el día de hoy a nuestra Asociación Médica de Puerto Rico, a todo el pueblo de Puerto Rico, sus instituciones gubernamentales, cívicas o de otra índole,

para ayudar y colaborar en todo aquello que sea de beneficio a la salud de nuestro pueblo.

Me siento muy feliz porque les tengo a todos ustedes, mis compañeros, para ayudarme a mantener en alto ese glorioso estandarte de nuestra Asociación, que es orgullo de todos nosotros.

Muchas gracias.

CORRECT ANSWER TO MEDI-QUIZ

1. D, E
2. C, D
3. E
4. A

NOTA BIOGRAFICA



DR. ANTONIO DE THOMAS

Presidente, Asociación Médica de Puerto Rico

1980

Nació el doctor De Thomas en la ciudad de Nueva York el 7 de junio de 1932. Realizó sus estudios de escuela superior en la Escuela Superior Central de Santurce y su Bachillerato en la Universidad Interamericana.

Sus estudios de medicina los realizó en la Escuela de Medicina de la Universidad de Barcelona, España, donde obtuvo su Doctorado en Medicina y Cirugía en el año 1961. Realizó su Internado en el Hospital Municipal de San Juan del 1962 al 1963.

Se especializó en Siquiatría en el Departamento de Siquiatría de la Escuela de Medicina de la Universidad de Puerto Rico durante los años 1966 a 1969.

Es miembro, entre otras, de la Asociación Médica Americana, Asociación Siquiatría Americana, Asociación Puertorriqueña de Graduados en Universidades Españolas y de la Sección de Siquiatría, Neurología y Neurocirugía de la Asociación Médica de Puerto Rico. Ha participado en numerosos Consejos y Comités de la Asociación. En 1976 fue electo Presidente de la Sociedad Médica del Distrito Este, en 1978 Vice-Presidente de la Asociación y en 1979 ocupó la Presidencia de la Cámara de Delegados de la AMPR.

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If that is what you want, join the physicians who have joined the Army. Army Medicine is the perfect setting for the dedicated physician. Army Medicine provides wide-ranging

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La Junta Editora, consciente de su responsabilidad de hacer que el "Boletín" cumpla a cabalidad con su cometido de divulgar conocimientos médicos, elevar las normas de educación médica y al propio tiempo de llenar las necesidades de todos los compañeros médicos, ha acordado establecer una nueva Sección que se conocerá como "Sección de Preguntas".

Bajo esta nueva Sección, todos los compañeros tendrán la oportunidad de enviarnos preguntas médicas de casos difíciles o casos clínicos para opinión experta. Estas preguntas, con sus respuestas, serán publicadas en esta nueva Sección.

Las preguntas deberán ser enviadas a:

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Esperamos sus preguntas.

Juan M. Aranda, MD
Presidente
Junta Editora

TYLENOL® with Codeine

tablets  / elixir 



mild to
moderate pain



moderate to
severe pain

Summary of Prescribing Information

Description

Tablets: Contain codeine phosphate*: No. 1—7.5 mg. ($\frac{1}{8}$ gr.); No. 2—15 mg. ($\frac{1}{4}$ gr.); No. 3—30 mg. ($\frac{1}{2}$ gr.); No. 4—60 mg. (1 gr.)—plus acetaminophen 300 mg.

Elixir: Each 5 ml. contains 12 mg. codeine phosphate* plus 120 mg. acetaminophen (alcohol 7%).

*Warning: May be habit forming.

Actions: Acetaminophen is an analgesic and antipyretic; codeine an analgesic and antitussive.

Contraindications: Hypersensitivity to acetaminophen or codeine.

Warnings: Drug dependence. Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration, prescribe and administer with same caution appropriate to other oral narcotics. Subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Caution patients that codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with this drug may exhibit additive CNS depression. When such a combination is contemplated, reduce the dose of one or both agents.

Usage in pregnancy: Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Pediatric use: Safe dosage of this combination has not been established in children below the age of three.

Precautions: Head injury and increased intracranial pressure: Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: Codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients: Administer with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: Most frequent, lightheadedness, dizziness, sedation, nausea and vomiting, more prominent in ambulatory than nonambulatory patients, some of these reactions may be alleviated if the patient lies down. Others: euphoria, dysphoria, constipation and pruritus.

Dosage and Administration: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. TYLENOL with Codeine tablets are given orally. The usual adult dose is: Tablets No. 1, No. 2, and No. 3: One or two tablets every four hours as required. Tablets No. 4: One tablet every four hours as required. TYLENOL with Codeine elixir is given orally. The usual doses are **Children (3 to 6 years):** 1 teaspoonful (5 ml.) 3 or 4 times daily; **(7 to 12 years):** 2 teaspoonful (10 ml.) 3 or 4 times daily; **(under 3 years):** safe dosage has not been established. **Adults:** 1 tablespoonful (15 ml.) every 4 hours as needed.

Drug Interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings. For information on symptoms/treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing.

TYLENOL with Codeine tablets are manufactured by McNeil Laboratories Co., Dorado, Puerto Rico 00646.

Caution: Federal law prohibits dispensing without prescription.

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08721

McNEIL

McNeil Laboratories, McNEILAB, Inc.
Fort Washington, PA 19034

In Fractures

Potent pain relief without aspirin complications



TYLENOL[®] with Codeine

tablets  / elixir 

Tablets Contain acetaminophen 300 mg plus codeine phosphate* as follows:
No. 1—7.5 mg (1/8 gr); No. 2—15 mg (1/4 gr); No. 3—30 mg (1/2 gr); No. 4—60 mg (1 gr)
Elixir Each 5 ml contains 12 mg codeine phosphate* plus 120 mg acetaminophen (Alcohol 7%)

*Warning: May be habit forming

Please see facing page for summary of prescribing information

"It hurts when I do this."



In diagnosing work-related musculoskeletal disorders, such as low back pain, it is often helpful to have the patient simulate the motions he does at work.

Dual-acting **PARAFON FORTE**[®] (chlorzoxazone 250 mg plus acetaminophen 300 mg) **tablets**

promptly relieves both pain and spasm^{*}

In acute musculoskeletal conditions,^{*}
PARAFON FORTE tablets are:

Dual-acting

combining the effective pain relief^{1,2} and safety³⁻⁵
of **TYLENOL**[®] acetaminophen and the muscle-spasm
reduction of chlorzoxazone

Prompt-acting

clinical studies have shown that patients respond by
the first evaluation period (day 2)^{6,7}

Minimally sedating

clinical studies have shown that most patients
remain mentally alert when the drug is administered at
recommended doses^{7,8}

Specify no substitution

to make sure your patients get the quality
of the PARAFON FORTE brand

DEPOT STOCKED 500's
Military 6505-00-764-3313
VA 6505-00-764-3313A

Summary of Prescribing Information

***Indications:** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective as an adjunct to rest and physical therapy for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Chlorzoxazone does not directly relax tense skeletal muscles in man.

Contraindications: Sensitivity to either component.

Warnings: Usage in Pregnancy—Use in women of childbearing potential only when potential benefits outweigh possible risks.

Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped.

Adverse Reactions: Occasionally, drowsiness, dizziness, light-headedness, malaise, overstimulation or gastrointestinal disturbances may be noted; rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, chlorzoxazone may possibly have been associated with gastrointestinal bleeding. While **PARAFLEX**[®] (chlorzoxazone) tablets and other chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately twenty-seven patients, it was not possible to state that the dysfunction was or was not drug induced.

Usual Adult Dosage: Two tablets q.i.d.

Supplied: Light green tablets, imprinted "McNEIL" and "PARAFON FORTE"—bottles of 100 and 500.

0972

Caution: Federal law prohibits dispensing without prescription. Full directions for use should be read before administering or prescribing.

For information on symptoms/treatment of overdosage, see full prescribing information.

PARAFON FORTE tablets are manufactured by McNeil Laboratories Co., Dorado, PR 00646.

References: 1. Wallenstein SL, Houde RW. *Fed Proc* 13:414, 1954. 2. Batterman RC, Grossman AJ. *Fed Proc* 14:316, 1955. 3. Vickers FN. *Gastrointest Endosc* 14:94, 1967. 4. Fein FT. *Ann Allergy* 29:598, 1971. 5. Melke CH, et al. *JAMA* 235:613, 1976. 6. Vernon WG. *Curr Ther Res* 14:801, 1972. 7. Miller AR. *Curr Ther Res* 19:444, 1976. 8. Walker JM. *Curr Ther Res* 15:249, 1973.

McNEIL

McNeil Laboratories
McNEILAB, Inc., Fort Washington, PA 19034



Tail of whipworm
(*Trichuris trichiura*)

Vermox®: the only anthelmintic highly effective against whipworm.

	Cure Rate	Egg Reduction
VERMOX®	68% *	93% **
Mintezol ¹	35% †	45% ††
Antiminth ²	Not Indicated	
Povan ³	Not Indicated	

Also highly effective against roundworm and hookworm

Since whipworm, roundworm and hookworm are all soil-borne helminths, mixed infections are not uncommon. Only one anthelmintic exhibits high efficacy rates for all three nematodes: whipworm—68%; roundworm—98%; hookworm—96%. That agent is VERMOX®.

Please see following page for Summary of Prescribing Information.

**Broad-spectrum coverage
in mixed helminthic infections**

Vermox® TABLETS
(mebendazole)



JANSSEN PHARMACEUTICA INC.
New Brunswick, N.J. 08903

*Committed to research...
because so much remains to be done.*

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JPI-023



**Broad-spectrum
coverage in mixed
helminthic infections**

Vermox[®] TABLETS
(mebendazole)

Contraindications VERMOX is contraindicated in pregnant women (see: Pregnancy Precautions) and in persons who have shown hypersensitivity to the drug.

Precautions **PREGNANCY:** VERMOX has shown embryotoxic and teratogenic activity in pregnant rats at single oral doses as low as 10 mg/kg. Since VERMOX may have a risk of producing fetal damage if administered during pregnancy, it is contraindicated in pregnant women.

PEDIATRIC USE: The drug has not been extensively studied in children under two years; therefore, in the treatment of children under two years the relative benefit/risk should be considered.

Adverse Reactions Transient symptoms of abdominal pain and diarrhea have occurred in cases of massive infection and expulsion of worms.

Dosage and Administration The same dosage schedule applies to children and adults. The tablet may be chewed, swallowed or crushed and mixed with food. For the control of pinworm (enterobiasis), a single tablet is administered orally, one time.

For the control of roundworm (ascariasis), whipworm (trichuriasis), and hookworm infection, one tablet of VERMOX is administered, orally, morning and evening, on three consecutive days.

If the patient is not cured three weeks after treatment, a second course of treatment is advised. No special procedures, such as fasting or purging, are required.

* Mean cure rate of VERMOX[®] in treating whipworm; cure rate range of 61-75%. Data on file at Janssen Pharmaceutica Inc.

** Mean egg reduction of VERMOX[®] in treating whipworm; egg reduction range of 70-99%. Data on file at Janssen Pharmaceutica Inc.

† Rollo, I.M.: Drugs used in the chemotherapy of helminthiasis, in Goodman, L.S.; and Gilman, A. (eds.): *The Pharmacological Basis of Therapeutics*, ed. 5. New York, Macmillan, 1975, p. 1034.

†† Miller, M.J.; Krupp, I.M.; Little, M.D.; Santos, C.: Mebendazole an effective anthelmintic for trichuriasis and enterobiasis. *JAMA* 230 (10): 1412-1414, Dec. 9, 1974.

1. Registered trademark of Merck Sharp and Dohme.
2. Registered trademark of Roerig.
3. Registered trademark of Parke-Davis.



JANSSEN PHARMACEUTICA INC.
New Brunswick, N.J. 08903

*Committed to research...
because so much remains to be done.*



Lung cancer is now an equal opportunity tragedy.

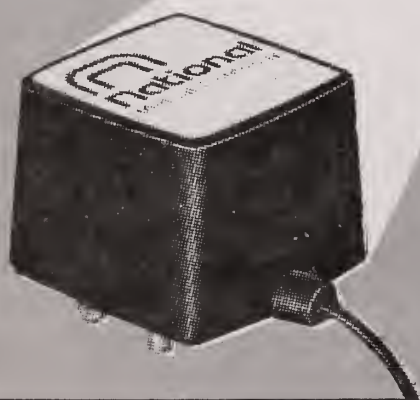
Remember when lung cancer was a man's disease. Because men had been smoking longer than women. But the women's smoking boom that started in the 1930's and 40's—is paying most cruel dividends today. Yet most people still think lung cancer is a man's disease. Tell your female patients the true story. That lung cancer is now an equal opportunity tragedy. That's what "you've come a long way, baby" is all about.

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CLINICAL AND MANOMETRIC EFFECTS OF NIFEDIPINE IN PATIENTS WITH ESOPHAGEAL ACHOLASIA

Mauro Bortolotti and Giuseppe Lab. *Gastroenterology* 80: 39-44, 1981.

Nifedipina disminuye el movimiento de calcio hacia el interior celular. Este antagonista disminuye el tono de la musculatura arterial y relaja las células de músculo liso. Los autores evaluaron nifedipina en veinte pacientes con acalasia esofágica leve o moderada. Dosis de 10 a 20 mg sublingual redujeron la presión del esfínter inferior esofágico por más de una hora. En un estudio clínico usando tales dosis media hora antes de las comidas se encontró una mejoría significativa en síntomas con resultados excelentes o buenos en la gran mayoría de los pacientes.

(Sometido por A. Olazábal, MD, VAH)

FEMORAL NERVE PALSY, COMPRESSION BY LYMPH GLANDS IN INGUINAL REGION

Khella L. - *Arch Phys Med Rehab* 60: 325-326, 1979.

La neuropatía femoral causada por compresión del nervio femoral no es un síndrome común cuando se compara con otras neuropatías compresivas. En la mayoría de los casos reportados, la compresión ha sido intraabdominal, ya sea retroperitoneal o en el curso del nervio a través del músculo psoas mayor. En este caso, la compresión fue producida

por nódulos linfáticos inguinales. La electromiografía y los estudios de conducción nerviosa revelaron que la lesión era neurapraxica. Como se esperaba, la condición fue reversible, el paciente respondió al tratamiento de las glándulas inflamadas y a terapia física. El uso de EMG fue útil para confirmar el diagnóstico y decidir el pronóstico.

(Sometido por Jesús A. Maldonado, MD, VAH)

EPIDEMIC NEONATAL GENTAMICIN-METHICILLIN-RESISTANT STAPHYLOCOCCUS AU-REUS INFECTION ASSOCIATED WITH NON-SPECIFIC TOPICAL USE OF GENTAMICIN

Donald R. Graham, MD, Adolfo Correa-Villasenor, MD, Roger L. Anderson, PhD, John H. Vollman, MD, and William B. Baine, MD, (*The Journal of Pediatrics*, Vol 97, No. 6, pp. 972-978)

In recent years strains of staphylococcus aureus have become resistant to methicillin or gentamycin. The authors report findings in a large outbreak of neonatal infection caused by *S. aureus* resistant to gentamycin and methicillin which occurred in a 59 bed neonatal intensive care unit of a 253 bed children's hospital in 1978.

One hundred sixteen infants acquired staphylococcus aureus resistant to gentamycin and methicillin. Topical application of gentamycin was significantly associated with acquisition of the gentamycin-methicillin resistant staphylococcus aureus. Of 78 infants who acquired the organism 38 had received gentamycin ointment before GMRS was first cultured, where as only one of 49 infants with GMRS had previously received gentamycin ointment. Infants with GMRS were more likely to have lower mean birth weight, Apgar Score and gestational age, pro-

long systemic antibiotic therapy and incubator care. These factors did not explain susceptibility to GMRS infection. Multivariate logistic regresion analysis showed that the use of gentamycin ointment was the single most important risk factor. Antibiotic ointments should be used only when specifically indicated.

(Sometido por M. Valcárcel, MD)

AUTONOMIC HYPERREFLEXIA: PATHOPHYSIOLOGY AND MEDICAL MANAGEMENT

Erickson, R. P. - Arch Phys Med Rehab 61: 431-440, 1980.

El manejo rápido y adecuado de la hiperreflexia autonómica es integral en la rehabilitación de pacientes con mielopatías. Más del 80 por ciento de los pacientes tetrapléjicos y parapléjicos exhiben este síndrome durante su proceso rehabilitativo. La prevención exitosa y el manejo requiere una clara comprensión de la patofisiología. La prevención se logra a través del cuidado médico general óptimo y del manejo adecuado de vejiga urinaria, intestino y piel. El tratamiento del episodio agudo requiere una rápida identificación y remoción del agente causal y, ocasionalmente, la administración de un vasodilatador directo potente (diazóxido, nitroprusiato). Los episodios recurrentes se manejan por medio del manejo definitivo del problema primario y se acompaña de una prevención sintomática del síndrome (mecamilamina, fenoxibenzamina).

(Sometido por Jesús A. Maldonado, MD, VAH)

FRACTURES IN PATIENTS WITH MYOPATHIES

Hirotsu H, Doko S, Fukunaga H, Yamamoto I, Morita R, Torizuka K, Yoshioka C - Arch Phys Med Rehab; 178-182, 1979.

En los últimos 4 años, se encontraron 15 fracturas en 10 pacientes de 48 hospitalizados por miopatías. Los sitios de predilección fueron el fémur (supracondilar) y el húmero (sub-capital). Evaluando el volumen total de potasio del cuerpo, el contenido mineral del hueso, el calcio sérico, fósforo inorgánico, vitamina D₃, la hormona paratiroidea y calcitonina, se concluye que la tendencia a la fractura en pacientes con miopatía es causada por atrofia ósea que obedece a la falta de tensión muscular relacionada con una disminución en el volumen muscular.

(Sometido por Miguel A. Berrios, MD, VAH)

DOUBLE-BLIND CROSS-OVER STUDY COMPARING LOPERAMIDE, CODEINE, AND DIPHENOXYLATE IN THE TREATMENT OF CHRONIC DIARRHEA

K. R. Palmer, C. L. Corbett, and C. D. Holdsworth - Gastroenterology 79: 1272-1275, 1980.

Se compararon estas tres drogas (loperamide o Imodium.® codeína, y difenoxylate con atropina o Lomotil.®) en treinta pacientes con diarrea crónica. Los pacientes recibieron los tres medicamentos cada uno por cuatro semanas. Se instruyó a los pacientes a subir la dosis del medicamento hasta controlar los síntomas o que los efectos secundarios fueran intolerables. se encontró que los tres medicamentos reducían la frecuencia de evacuar, pero que difenoxilato: 1. era menos efectivo en producir una excreta sólida, 2. era menos efectivo en reducir la incontinencia fecal; y 3. produjo más síntomas nocivos secundarios. Los autores concluyeron que loperamida y codeína son superiores a difenoxilato en el tratamiento del paciente sintomático con diarrea crónica.

(Sometido por Angel Olazábal, MD)

STRESS MANAGEMENT FOR REHABILITATION CLIENTS

Goodwin, Lloyd R, *Rehabilitation Counseling Bulletin* March 1980, 23: 3: 193-201.

"Stress", la respuesta general del cuerpo a una situación que demanda reajuste y adaptación, es un factor importante en el comienzo, progreso, y tratamiento de casi toda incapacidad. Este artículo discute como consejeros de rehabilitación pueden ayudar a los clientes a manejar el "stress" para evitar el comienzo de nuevas enfermedades, ajustarse a las incapacidades existentes, y mejorar la calidad de vida. Después de una consideración de desórdenes causados por "stress", y de los patrones de reacción de pacientes y familiares a una incapacidad, fuentes de ansiedad y de "stress" en rehabilitación son identificadas. La respuesta neurofisiológica innata al "stress" y una respuesta análoga fisiológica que permite a la persona relajarse son explicadas. Educar a personas incapacitadas a relajarse por métodos como meditación, yoga, bio-feedback, y training autogénico es sugerido.

(Sometido por Rafael Alvarez, MD)

RECREATIONAL ACTIVITIES OF LOWER EXTREMITY AMPUTEES: A SURVEY

Kegel B, Webster JC, Burgess EM - *Arch Phys Med Rehab* Vol 61: 258-264, 1980.

Este estudio resume una evaluación por cuestionario detallada de actividades recreacionales en que participaron 100 personas con amputaciones de extremidad inferior. Información adicional se obtuvo de prostetistas y terapeutas físicos. Aproximadamente 69 por ciento de los que respondieron son activos en deportes. Personas jóvenes de cualquier sexo que han sufrido amputaciones por trauma o deformida-

des congénitas son los más activos. El nivel de amputación no parece ser un factor determinante en si el amputado participa o no. Las actividades recreacionales más comunes son la natación y la pesca. Los deportes que producen más molestias al amputado son la caza y el "jogging". La habilidad para correr y brincar es la más difícil de lograr. Razones para no participar son el dolor, la timidez, entrenamiento insuficiente y la falta de programas deportivos organizados para el incapacitado. Miedo a lastimarse o la familia sobreprotectora no son factores inhibidores, ni tampoco es el costo de la prótesis. Solamente muy pocos utilizan una prótesis especialmente diseñada para recreación y solamente un tercio de los amputados creen que el prostetista les desalienta las ideas prostéticas innovadoras. Terapeutas también demostraron ser inadecuados en conocimiento y esfuerzo a preparar al amputado para la recreación. Los amputados indicaron una necesidad para mejora de diseño prostético y creen no recibir suficiente información verbal y escrita.

(Sometido por Rafael Alvarez, MD)

SEMIMEMBRANOUS INSERTION SYNDROME: A TREATMENT AND FREQUENT CAUSE OF PERSISTENT KNEE PAIN

Weiser, Hans I. MD, *Arch Phys Med Rehab* Vol 60: 317-319, 1979.

El síndrome de la inserción semimembranosa causa dolor en el aspecto medial de la rodilla. Este dolor empeora con el ejercicio o la flexión brusca de la rodilla. El paciente refiere dolor a la palpación, inflamación en la porción distal de los Hamstrings mediales y dolor en la rotación pasiva de la rodilla. Si se ejerce presión con el dedo en la inserción del tendón semimembranoso se presenta un dolor exquisito.

El tratamiento con calor o ejercicios agra-

van el dolor. Un centenar de pacientes con esta condición consiguieron alivio temporero con inyección local de lidocaína con triancinolona. Alivio más duradero se consiguió en 58 pacientes, en 30 de estos fue necesario repetir la inyección en 3-5 meses. En

9 pacientes disminuyó el dolor y mejoró su incapacidad. En 18 el seguimiento no tuvo éxito y en 15 pacientes no hubo seguimiento.

(Sometido por Rafael Aguayo, MD)

In Hypertension*...When You Need to Conserve K⁺

Every Step of the Way



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

EFFECTIVE STEP 1 DIURETIC THERAPY[†] (when the combination represents previously titrated dosage)

[†]Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K⁺ supplement or K⁺-sparing agent) and a maintenance phase (a diuretic alone or in combination with a K⁺ supplement or K⁺-sparing agent).

Serum K⁺ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, throm-

bocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K⁺ frequently, both can cause K⁺ retention and elevated serum K⁺. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Anti-hypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transiently elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with

possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

Supplied: Bottles of 1000 capsules. Single Unit Packages (unit-dose) of 100 (intended for institutional use only), in Patient-Pak™ unit-of-use bottles of 100.

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When you choose Limbitrol over a phenothiazine-containing product, you minimize the risk of tardive dyskinesia — now associated even with low dose, short-term phenothiazine therapy.^{1,2} You also reduce the possibility of other extrapyramidal side effects, which occur in approximately 30% of patients receiving phenothiazines.³⁻⁵ In contrast, the reported incidence of these disturbing reactions with Limbitrol or either of its compo-

nents alone is rare. (For a complete list of side effects reported with Limbitrol, please consult full disclosure.)

References: 1. Paulson GW. *NY State J Med* 79: 193-195, Feb 1979. 2. Hallister LE. Antipsychotic medications and the treatment of schizophrenia, chap. 9, in *Psychopharmacology from Theory to Practice*, edited by Barchas JD, et al. New York, Oxford University Press, 1977 pp 134, 145. 3. Domino EF. Antipsychotics phenothiazines, thioxanthenes, butyrophenones, and rauwolfia alkaloids, chap. 25, in *Drill's Pharmacology in Medicine*, ed. 4, edited by DiPalma JR. New York, McGraw-Hill Book Company, 1971, p. 476. 4. Savner R, DiMascia A. Extrapyramidal syndromes and other neurological side effects of psychotropic drugs, in *Psychopharmacology: A Generation of Progress*, edited by Lipton MA, DiMascia A, Killam KF. New York, Raven Press, 1978, p. 1021. 5. Donlan PT, Stenson RL. *Dis Nerv Syst* 37: 629-635, Nov 1976.



SAFETY/BENEFIT RATIO



What
better reason
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Limbitrol
for your
patients with
moderate depression and anxiety?

Limbitrol[®] IV

Tablets 5-12.5 each containing 5 mg clordiazepoxide and 12.5 mg amitriptyline
(as the hydrochloride salt)

Tablets 10-25 each containing 10 mg clordiazepoxide and 25 mg amitriptyline
(as the hydrochloride salt)



Efficacy without a phenothiazine

Please see summary of product information on following page.

LIMBITROL® TABLETS Tranquilizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety.
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use. Then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated.

Sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy.

Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) — bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10, Prescription Paks of 50.

How to initiate and maintain therapy

Select dosage strength appropriate for each patient

- Limbitrol 5-12.5 is recommended to minimize drowsiness and for elderly patients
- Limbitrol 10-25 may be indicated for patients who tolerate medication without undue side effects

Specify daily dosage based on symptom severity

- An initial dosage of three tablets is recommended
- Dosage may be increased to six tablets or decreased to two tablets daily as necessary
- Once a satisfactory response is obtained, patients should be continued on the smallest dose required to maintain the desired effect

Utilize dosage options to best accommodate individual patient needs

- T.I.D. or Q.I.D., familiar regimens most suited for patients who tolerate medication without undue drowsiness
- Two tablets one hour before bedtime and one tablet midday may minimize daytime drowsiness and help relieve a common target symptom — insomnia
- Entire dosage h.s. to take maximum advantage of the sedative effect

Your guide to patient management... when you decide medication is needed

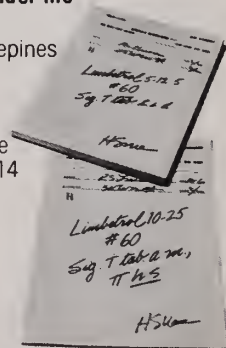
How to make each patient an informed patient

1. Discuss with patients the probability that they will experience drowsiness, especially during the first week.
2. Reassure your patients that drowsiness is one indication that the medication is working and that it may help alleviate their insomnia.
3. Encourage patients to report if drowsiness becomes troublesome so that, if necessary, dosage schedule can be adjusted.
4. Caution patients about the combined effects with alcohol or other CNS depressants. Let them know that the additive effects may produce a harmful level of sedation and CNS depression.
5. Caution patients about activities requiring complete mental alertness, such as operating machinery or driving a car.
6. Warn pregnant patients and patients of childbearing age that the safety of Limbitrol in pregnancy has not yet been established.

Please see complete product disclosure for other pertinent information.

Limbitrol should not be used under the following circumstances:

1. Hypersensitivity to benzodiazepines or tricyclic antidepressants.
2. Concomitantly with an MAO inhibitor. To replace an MAO inhibitor with Limbitrol, discontinue MAO inhibitor for a minimum of 14 days before cautiously initiating Limbitrol therapy.
3. During the acute recovery phase following myocardial infarction.



In moderate depression and anxiety

Limbitrol®^{IV}

Relief without a phenothiazine

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A LA MEMORIA DEL:

DR. RAMON FERNANDEZ MARINA
1909 – 1981

Murió donde había nacido - en San Juan. Puerto Rico perdió su pionero del psicoanálisis. Aunque otros quehaceres le dan derecho propio para la connotación de su muerte.

Después de estudiar premédica en Maryland, se hace médico en Madrid en el 1933 y, por algunos años, practica la medicina en varios pueblos donde se le recuerda con admiración y cariño. En Washington hace su residencia en psiquiatría y termina sus estudios de psicoanálisis en el 1948 cuando regresa a Puerto Rico a hacer su máxima aportación.

Dirige el Hospital de Psiquiatría por varios años intentando soluciones heroicas — a veces maquiavélicas — pero siempre innovadoras. También dirige el Hospital Psiquiátrico de Hato Tejas desde el 1952 al 1970. Así también el Instituto Psiquiátrico donde crea y dirige la primera residencia psiquiátrica en Puerto Rico.

Practica, enseña y aporta a la ciencia psiquiátrica que fue el centro de su actividad, pero no la única.

Primer miembro puertorriqueño de la Asociación Psicoanalítica Americana y de la Psicoanalítica Internacional, siempre recordaré la noche en que recibió dicho galar-

dón — lo que me comunicó en una reunión de médicos, diciéndome: “si lo comento con otros dirán, ¿y qué es eso?”

Receptor de numerosos premios y menciones, trabajó hasta el final como era su deseo. Como educador medró siempre hacia la excelencia. A pesar de la acogida con beneplácito y loor de sus libros y artículos dentro del campo psiquiátrico, más se deleitaba en participar en concursos de poesía popular, llegando a manejar la décima y la improvisación con donaire. Galardoneaba sus premios en el campo de la poesía con mayor deleite que sus triunfos en la medicina, la psiquiatría y el psicoanálisis.

Buen conferenciante y conversador ameno — jamás se le encontró aburrido. Buen clínico, eminente terapeuta, se mantuvo moderno hasta perder su lucha por la vida.

Buen padre, mejor abuelo, saboreó la consumación de una vida.

Para nosotros los que laboramos con él y de los que fue mentor en el Instituto Psiquiátrico de Puerto Rico, su recuerdo será siempre inspirador — ahito de añoranzas.

Víctor Bernal y del Río, MD

N O T I C I A S

AMA NEWS:

THYROID SUPPLEMENTS VARY WIDELY IN POTENCY

CHICAGO — Different brands of a thyroid supplement can vary considerably in potency, says a report in the Oct. 10 Journal of the American Medical Association.

Sheldon S. Stoffer, MD, of Southland, Mich., reports on an analysis of a brand name thyroxine tablet and two generic products, supposedly the same.

The thyroxine content was significantly different in the generic tablets when compared with the brand name product, Dr. Stoffer says. Even the brand name had only 78 per cent of expected potency, he found.

Manufacturers should be required to measure the thyroxine content of their tablets, the Michigan researcher recommends. However, the patient who sticks with one particular brand will be able to adjust the dosage to achieve the desired balance of thyroid output. But he might be in trouble if he switches to a supposedly equivalent generic product in an effort to save money, Dr. Stoffer declares.

"Until such time that levothyroxine products become more uniform, physicians, pharmacists, and legislators should not encourage product switching," he concludes.

Legislation has been introduced in some governmental units to require use of the least expensive medication in an effort to save money.

HIGH BLOOD PRESSURE DRUG BRINGS CHOLESTEROL RISE

CHICAGO — In a report in the Oct. 10 Journal

of the American Medical Association, researchers found that a drug that has been used successfully to reduce mild high blood pressure is causing an increase in cholesterol. But they don't yet know how serious a health problem this is.

Mild high blood pressure brings increased risk of stroke and heart attack. Thus, it is advisable to bring down the pressure, if possible. Drugs can do this quite satisfactorily.

But increased cholesterol levels in the blood are associated with increased risk of coronary heart disease. Thus, it is wise to avoid anything that might bring an increase in cholesterol. And this now includes the drugs that control mild high blood pressure — chlorothalidone, or Hygroton, and reserpine.

The finding stems from a Veterans Administration-National Heart, Lung and Blood Institute Cooperative Study on Antihypertensive Therapy: Mild Hypertension. A total of 1,012 men and women, 21 to 50 years of age, with somewhat elevated blood pressure, were divided into two groups. Half received the drugs to bring down the blood pressure, the others a placebo. After a year of treatment the drugs group showed somewhat elevated cholesterol levels.

Heading the research team is Anne I. Goldman, Ph.D., of the University of Minnesota, Minneapolis.

Dr. Goldman points out that the effects of the drug-induced increase in cholesterol level on illness and death are unknown. The average increase is around 5 per cent, small but not insignificant. There is no evidence at present that a drug induced increase in cholesterol can raise the risk of heart attack, she says.

The possible net effect on risk of increasing cholesterol while lowering pressure in the long-term treatment of mild hypertension with drugs must be further evaluated, Dr. Goldman concludes.

NEW TEST TO DETECT POTENTIAL BIRTH DEFECTS RAISES PROBLEMS

CHICAGO — Progress in medicine sometimes raises new problems.

The Impact Section of American Medical News, the American Medical Association's newspaper for physicians, offers an analysis in the Jan. 30 issue of one of the newer advances in medicine that also brings new problems.

The development is a new diagnostic technique for determining early in pregnancy whether the infant may suffer from a serious birth defect.

The Food and Drug Administration has proposed rules for marketing and use of kits which measure the concentration of alpha-fetoprotein (AFP) in maternal blood and amniotic fluid. This will permit doctors to determine in advance whether the fetus is at high risk of anencephaly and spina bifida. In anencephaly, the brain develops only minimally. In spina bifida, the bony tissue surrounding the spinal cord does not close.

Two conditions often are termed neural tube defects (NTD). About 5,000 babies are born with NTD each year in this country. About half have anencephaly and die quickly. The range of severity in spina bifida is extremely wide, varying from mild walking problems to paralysis and mental retardation.

The testing procedure was widely adopted in Great Britain three years ago. About two-thirds of women in Scotland and about one-third of those in England are being tested, and birth of affected infants is dropping sharply.

One problem with the procedure is that the initial test will indicate those pregnancies at a higher risk for neural tube defects, but second tests will show that most of these pregnancies are normal. Furthermore, subsequent testing requires careful timing as well as performance of other tests, such as ultrasonography and amniocentesis, an invasive procedure which itself carries some degree of risk to the fetus. Of 1,000 pregnant U. S. women, only one or two would be found to have fetuses with neural tube defects. FDA proposed rules would require completion of the full range of tests if a woman shows an elevated AFP in initial testing.

To complicate the issue even more, the mother who learns she is likely to give birth to a defective infant has only one choice to prevent it — elec-

tive abortion. There is widespread organized opposition to elective abortion under any circumstances.

Author of the report is Philip Reilly, a graduate attorney who is now completing his third year at Yale Medical School, and has written a book, "Genetics, Law and Social Policy." Mr. Reilly declares:

"Certainly the AFP technology is posing moral, ethical, and legal problems that are complex. In my opinion, the screening technology is here to stay. The British success in using serum screening to reduce the number of children born with neural tube defects is extremely impressive."

The American Medical Association's House of Delegates at its San Francisco meeting last month adopted a report expressing opposition to proposed FDA rules to strictly regulate AFP testing, calling it "unwarranted intrusion into the practice of medicine." The AMA urged that pilot studies be conducted to determine the feasibility and desirability of mass screening programs of all expectant mothers for neural tube defects.

OVERDOSE OF ANTACIDS CAUSES SEVERE ILLNESS

CHICAGO — Don't overdo the antacids for upset stomach. You might come down with osteomalacia.

Osteomalacia isn't much fun. It involves extreme weakness, softening of the bones, muscle fatigue, pain.

Karl L. Insogna, MD, reports in the Dec. 5 Journal of the American Medical Association on the case of a 60-year-old woman who had been taking a magnesium-aluminum hydroxide liquid antacid (Malaolox) for 12 years. She had an internal condition that produced a burning pain in the stomach. In the early years she took some 4 ounces daily of the medicine, but for at least the final six months prior to entering Strong Memorial Hospital, Rochester, N. Y.,

she had been taking 12 or more ounces each day.

Pains in her right knee and thigh had begun to develop some 18 months before she entered the hospital, and at hospitalization the patient was unable to walk without support because of extreme pains in the legs. One leg was fractured.

The big doses of antacid had caused the patient to develop a condition in which dietary phosphate could not be absorbed, and the body was severely depleted of this essential substance.

The use of antacids was discontinued immediately and the patient made a dramatic recovery. She was walking again unassisted and without pain in a few months. The fracture healed.

Physicians caring for the elderly should be especially aware of the complication of aluminum-containing antacids, Dr. Insogna points out. Antacids often are used by the elderly, and poor dietary habits put these individuals at increased risk of phosphate depletion. Early recognition can lead to safe and effective treatment, he says.

Dr. Insogna was with the University of Rochester School of Medicine and Dentistry at the time of the case. He is now at Yale University School of Medicine, New Haven.

Away from the hustle and bustle of the city, the business of IRMA IV, both scientific and social, will be conducted in a calm and completely informal manner. The San Juan-Puerto Rico Convention Bureau, the authority responsible for housing, has managed to acquire a special hotel rate that is approximately half of the regular season's rate. Puerto Rico is the hub of air transportation between North and South America, Europe and the Caribbean, for which reason early and confirmed travel reservations are recommended.

The scientific program is developing very well around suggestions from the IRMA members. Fifty-seven different themes were proposed, of which twenty-two were selected and approved by the Puerto Rico and American Medical Association for an accredited, post-graduate course of 36 hours in Category I, divided into twenty, two-hour seminars, and two, eight-hour mini-courses. The tuition for the course is included in the registration fee of \$275.00 for IRMA members. The seminars that will be given in the mornings are as follows:

1. TECA Seminar: Present State of EMG.
2. Australian Seminar: Rehabilitation in Neurotrauma.
3. American Lung Association Seminar: Chest Diseases and Rehabilitation.
4. Puerto Rico State Insurance Fund Seminar: Spinal Cord Injury-Prevention and Treatment of Complications.
5. University of Baylor (Houston)-Texas Institute of Rehabilitation and Research Seminar: Research in Rehabilitation.
6. Merck Sharp and Dohme Seminar: Rheumatoid Arthritis and Rehabilitation.
7. Dista Products Company - Eli Lilly and Company Seminar: Relief of Pain.
8. Japanese Seminar: A Metropolitan Rehabilitation Center - Problems and Solutions.
9. Muscular Dystrophy Association Seminar: Neuromuscular Disease Research.
10. Rehabilitation Through Hand Reconstruction.

IRMA IV - PRESS RELEASE

The Fourth World Congress of the International Rehabilitation Medicine Association (IRMA IV) will take place in San Juan, Puerto Rico, April 18-24, 1982.

San Juan, the Capital of Puerto Rico, was founded in 1521, and the metropolitan area has over one million inhabitants. There is a historical presence to this modern metropolis that tranquilizes the most troubled minds. The El San Juan Resort Center, situated in the Isla Verde Section, is a tourist complex of three outstanding hotels bordering one of the most beautiful beaches bathed by the Atlantic Ocean.

11. Stroke Rehabilitation.
12. Riker Laboratories Seminar: The Management of Arthritic Diseases.
13. Education.
14. Cardiac Rehabilitation.
15. New York University Seminar: The Neuromuscular Diseases.
16. University of Washington (Seattle) Seminar: Lower Extremity Orthotics.
17. Sandoz Pharmaceutical Seminar: Geriatrics and Rehabilitation.
18. Hato Rey Psychiatric Institute Seminar: Mental Illness and Rehabilitation.
19. Norwich-Eaton Pharmaceutical Seminar: Relief of Spasticity.
20. Therapeutic Exercises for the Training of Coordination.

The eight-hour courses are programmed for the afternoon. They are:

1. Puerto Rico Office of Vocational Rehabilitation Course: Return of Functions after Central Nervous System Trauma.
2. Veterans Administration Course: What's New in Prosthetics and Orthotics?

Additional sessions include: The Cordis-Hyperion Four-hour Course on Therapeutic Use of Electromyography, The World Health Organization Seminar on Prevention of Disability, and the American Cancer Society Seminar on Cancer Rehabilitation. Others will be programmed. The Scientific Program Committee has allocated 500 slots for individual papers of ten minutes each, to be grouped into specific seminars on different subjects. Posters sessions, scientific and technical exhibits, and a scientific film festival will round out the scientific program.

Puerto Rico is justly famous for its hospitality. Ask any one who has attended a convention or a congress in this beautiful island, called the Pearl of the Caribe. IRMA IV will prove no exception. A full week of entertainment, including a Puerto Rican Fiesta and rum parties, is planned, as the guest The Commonwealth of Puerto Rico and IRMA IV.

There will be two special affairs: The Sidney Licht Memorial Luncheon on Tuesday, April 20,

1982 and the IRMA IV Congress Banquet-Ball on Friday, April 23, 1982. The Sidney Licht Memorial Lecture, in honor of IRMA's founder, will be addressed by Mrs. Zala L. N'Kanza, Executive Secretary of the International Year for the Disabled Persons. Mrs. N'Kanza will discuss the programs presented to the Secretariat, IYDP from all over the world during 1981 for the first time to an international audience. Dr. Howard A. Rusk, the revered Father of Rehabilitation Medicine, will speak during the banquet, and his vast experience guarantees a sagacious, provocative as well as entertaining presentation.

The scientific and social programs bespeak a movable feast, a magnificent fiesta of learning, entertainment and friendship in Puerto Rico at IRMA IV, April 18-24, 1982. Please separate this date in your mind, mark your calendar and register now for IRMA IV. For registration, hotel reservation, abstract, and exhibit forms write to: Dr. Herman J. Flax, Chairman, IRMA IV, P. O. Box 11696, Caparra Heights Station, Puerto Rico, 00922 USA.

MORE AMA NEWS:

MORE STUDY NEEDED OF IMPLANTED INSULIN DEVICES FOR DIABETICS

CHICAGO — Caution in proceeding with implantation of an artificial pancreas as a potential cure for diabetes is voiced in a report in the Feb. 20 Journal of the American Medical Association.

Recently, successful diabetic treatment with implanted insulin delivery devices has accelerated efforts toward total implantation. Within months remotely controlled implantable insulin devices will be available to many specialists in diabetes.

MDs David S. Schade and R. Philip Eaton of the University of New Mexico School of Medicine, Albuquerque, ask: With more than five million diabetic patients in this country, should widespread, clinical implantation of these devices be started immediately? Drs. Schade and Eaton promptly answer their own question: Not yet.

There still are too many answers not yet available in implanted insulin delivery, the New Mexi-

co physicians point out. A major problem is to make absolutely certain the device is foolproof. If a sudden big surge of insulin were released, death would follow quickly.

There is no great urgency to being implanting devices that will release small amounts of insulin daily, thus freeing the diabetic from the need for regular injections of insulin. Those very injections are effective in controlling diabetes already, and the implantable devices are not required to keep diabetics alive, they point out.

If the device delivers just a little too much insulin, the result would be a weight gain to the point of obesity. Other unanswered questions concern the amount of insulin to be released per meal and appropriate dosage for each patient.

There is real hope that the problems will be solved, and "An optimistic approach would suggest that before the end of this decade, small safe, implantable insulin delivery devices will be available to diabetic patients in whom the complications of diabetes constitute a threat to life."

ACUPUNCTURE GAINS ACCEPTANCE AS TREATMENT FOR PAIN

CHICAGO — Acupuncture has gained acceptance with a small but growing number of American physicians as treatment for pain, says a report in the Feb. 20 Journal of the American Medical Association.

American doctors have been slow to accept acupuncture largely because it has been presented as fanciful theory based on ancient Taoist philosophy involving the two major forces of yin and yang affecting the bodily energy balance. Diagnosis is based on ritualistic palpation and interpretation of an imaginary 12 different radial pulses. Decisions for treatment are based on the legendary basic elements of fire, earth, metal, water and wood.

This makes for delightful reading in the history of Oriental medicine, but is not convincing to the Western trained physician, says George A. Ulett, MD, a St. Louis physician.

Also, with the initial publicity surrounding former President Nixon's visit to China, the media overreacted to this novel Oriental approach to medicine and publicized it widely as a cure-all. This it is not, and hence the initial flurry of excitement soon receded, Dr. Ulett declares.

There are some theories on how acupuncture works, but they have not been finally proved, he says.

Notwithstanding the early problems, a small but increasing number of U. S. physicians have found acupuncture to be a useful part of their practice, despite their inability to explain in terms acceptable to their colleagues how it works, Dr. Ulett reports.

"For those physicians faced with the necessity to treat patients with pain that is chronic and nonresponsive to the usual methods of chemical analgesia, acupuncture now seems a reasonable alternative."

Traditional acupuncturists select from among 400 or more points located on hypothetical meridians. Moderns have found that a much smaller number of points actually are needed to relieve pain. Many of these points on the body coincide with the points to which electrical leads are attached for measuring body activity, such as electrocardiograms. Some now think that acupuncture works by stimulating release of endorphins in the brains of humans. This is nature's substance for control of pain.

Much more remains to be learned about acupuncture, but "the evidence is now available to place this age-old Chinese healing art, modernized to U. S. standards, on a solid scientific base. There seems little doubt that acupuncture-type stimulation can and will play an increasingly important role in the relief of pain."

RADIATION TREATMENT MAY REPLACE BREAST REMOVAL

CHICAGO — A group of radiation therapists are becoming increasingly active in recommending to women with early breast cancer that they consider undergoing radiation therapy in conjunction with simple surgery to remove only the cancerous lump, rather than the entire breast.

Radiation therapy combined with surgery to remove the lump can achieve control rates that are comparable with those obtained by modified or radical mastectomy, declares Luther W. Brady, M. D., chairman of the Department of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College, Philadelphia.

The status of this procedure in treating early breast cancer is reviewed in the Medical News Section of the Feb. 20 Journal of the American Medical Association.

The combination surgery-radiation technique leaves the patient with two intact and cosmetically acceptable breasts, Dr. Brady emphasizes.

The acceptance of such breast-saving treatment has become even more important with the increase in detection of breast cancer at an early stage, adds Dr. Brady. He cites data showing that the pro-

portion of women whose disease was diagnosed prior to spreading to other parts of the body increased from 72 percent to 88 percent between 1970 and 1976.

The procedure is to remove the tumor (lumpectomy) and study the nearby lymph nodes for the presence of cancer. Then, a week or so later, irradiation of the breast is begun, continuing over a period of weeks. The patient may also be given anticancer drugs.

In one recent study of 293 patients, 71 percent of stage I patients and about half of stage II patients (signifying early and early intermediate stages of the cancer's growth) were alive and free of the disease ten years later. These figures compare with the 60 percent and 40 percent survival figures obtained with extensive surgery.

In writing of the new procedure among others, one research team declares: "The psychosocial advantages of any therapy that preserves the breast weighed heavily in our conclusion that primary radiotherapy is an acceptable alternative to mastectomy in many patients." Up to one-third of women after mastectomy suffer anxiety, depression and sexual difficulties.

A N U N C I O S

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Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective, as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma, prostatic hypertrophy, benign bladder neck obstruction, hypersensitivity to chlordiazepoxide HCl and/or clidinium Bromide.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium[®] (chlordiazepoxide HCl/Roche) to known addicts.

tion-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug.

and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, i.e., dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

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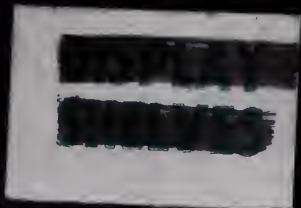
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BOLETIN

ASOCIACION MEDICA DE PUERTORICO

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EDITORIAL: SALT: A PRECIOUS SUBSTANCE WHICH MAY BE HARMFUL

SCREENING FOR INFECTION WITH *SCHISTOSOMA MANSONI* IN PUERTO RICO: A LIMITED SEROLOGIC SURVEY UTILIZING THE CIRCUMOVAL PRECIPITIN TEST

NOTAS HISTORICAS: MITRAL VALVE COMMISSUROTOMY BY JOHN ALEXANDER: REPEAT SURGERY 28 YEARS LATER

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GRAPHICS: ELECTROCARDIOGRAM OF THE MONTH

ABSTRACTOS DE LITERATURA MEDICA

CONSENSUS STATEMENT – FEBRILE SEIZURES: A CONSENSUS OF THEIR SIGNIFICANCE, EVALUATION, AND TREATMENT

NOTICIAS

INDICE PAGINA 48

VOLUMEN 73

NUM. 2

FEBRERO 1981

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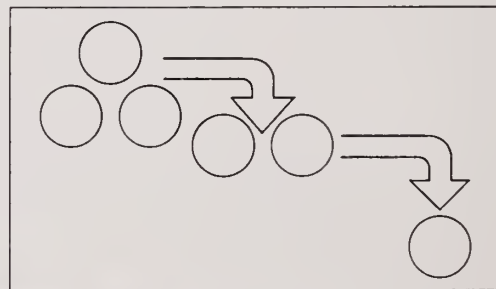
Elimination rates are gradual with Valium and thus provide a compatible adjustment interval for

the patient. In comparison, blood levels of short-acting agents with inactive metabolites decrease more rapidly and are more likely to be associated with withdrawal symptoms if medication is stopped abruptly.* With Valium unwanted effects other than drowsiness or ataxia are rare. Patients should be cautioned about driving and advised to avoid alcohol.

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*Sellers EM: *Drug Metab Rev* 8(1):5-11, 1978



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symptoms of anxiety*

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Before prescribing, please see summary of product information on next page

ROCHE

Valium® diazepam/Roche

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Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety, symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal, adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy)

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Use in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

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Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Medical Treatment Can Help Curb Acne

Acne Cure Elusive

Something can be done about acne. But beware the promise of a guaranteed cure. There are many, many approaches to treating the unsightly blackheads and pimples. But no one can promise a cure.

Acne is a common skin problem that affects most people to a varying degree and for a varying period during the teen years. But adults also can have acne.

Waiting to outgrow acne can be a serious mistake. Treatment by a physician can prevent the development of pitted scars and may improve appearance.

An American Medical Association pamphlet points out that basic research on the causes of acne links its occurrence to the biological changes that take place as young people mature. While acne usually clears after several years even if untreated, much can be done to minimize disfigurement. Treatment is a continuing process if the disorder is to be controlled successfully.

Acne is not caused by dirt,

but the sufferer may be told to wash frequently to cleanse the face of skin oils and hold down the formation of blackheads and pimples. Acne is not primarily a dietary disease, and authorities vary on the importance of diets in control of acne. One thing is certain: Following the strictest diet will not, by itself, clear your skin. Some people, however, find that their acne becomes worse when they eat small amounts of certain foods, particularly chocolate and fats.

Many nonprescription creams and lotions are available at drugstores. These may be of some benefit. Be certain to read the instructions and follow them.

Your doctor may make specific dietary suggestions. He probably will prescribe a preparation to be applied to your skin to help reduce oiliness and produce mild peeling. He may open inflamed lesions, and he may remove blackheads. Your doctor will most certainly warn you against picking, scratching, popping and squeezing.

Antibiotics often are prescribed for inflammatory acne. They reduce the bacteria in the skin. Anti-inflammatory cortisone-like drugs sometimes are prescribed.

No matter what the treatment, proper skin care by the individual is highly important.



October, 1980
Frank Chappell
Science News Editor
AMA

BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

(USPS-060000)

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Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Alcohol Absorbed Rapidly In The Body

Alcohol Absorbed

Alcohol is absorbed directly and fairly rapidly into the blood from the stomach and intestines. It is carried to the liver, then to the heart and distributed throughout the body's tissues.

Most consumed alcohol is eventually metabolized (broken down by body processes) into carbon dioxide and water.

A pamphlet from the American Medical Association points out that the rate of absorption varies among individuals and varies in the same person at different times. It depends on the amount of alcohol in the drink, how fast it is consumed, and how quickly it leaves the stomach.

Fasting or any other condition that causes rapid emptying of the stomach will bring about an increase in the absorption rate. Anything that delays emptying of the stomach, such as the presence of solid food, will retard absorption.

An average 150-pound man, under ordinary circumstances, can metabolize about seven grams of alcohol (the equivalent of about two thirds of an ounce of straight whiskey or eight ounces of beer) in an hour. But individual variation is reported to be as high as 50 per cent

more or less than the average. The more you drink beyond your ability to metabolize alcohol in a given period, the more intoxicated you become.

The most disturbing effects of alcohol occur in the central nervous system, especially the brain. Judgment, memory and learning ability all are affected as intoxication increases. Coordination is impaired, as reflected by unsteady gait, speech disturbances and reduced manual skill. The drinker may feel little pain, or may be unconcerned about his safety. High concentrations of alcohol can lead to shock and death.

Sustained exposure of brain tissue to alcohol ultimately can lead to destruction of brain cells. Inadequate diet, so often associated with alcoholism, probably contributes to this process as well as to the degeneration of nerve tissue.

Prolonged and heavy use of alcohol usually causes problems ranging from inflammation of the stomach to ulceration and internal bleeding. Many alcoholics develop cirrhosis of the liver.

Alcohol appears to constrict the arteries of the heart. Studies suggest that it can injure the heart muscle.

While the body seems to adapt gradually to increasing amounts of alcohol, this tolerance may be lost in the advanced stages of alcoholism. Drinkers then find they can no longer tolerate alcohol, and a relatively small amount can bring intoxication.



March, 1981
Frank Chappell
Science News Editor
AMA

EDITORIAL



EDITORIAL

THE FRANCIS & TAYLOR
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MAY 28 1981

SALT: A PRECIOUS SUBSTANCE WHICH MAY BE HARMFUL

Salt is everywhere around us and for centuries it was esteemed as a precious substance. Salt was used as money in China and in many parts of Africa and South America. At that time in Africa it was more valuable than gold, sometimes twice its weight in gold. In Greece it was used to purchase slaves and even today there are areas of the world in which salt is considered a relatively scarce commodity. In our advanced society with vast technological abilities salt is abundant and, indeed, is added to food in generous quantities. However, its widespread use may not be entirely harmless.

Estimates of salt requirements in man have ranged as high as 15 grams per day. However, misconceptions about requirements are common. Daily losses from the skin average 25 mg and with excessive sweating during the summer, healthy persons can maintain salt balance with intakes as low as 1.9 grams per day. Fecal losses may be minimal, in the range of 125 mg per day on a sodium intake of 4 grams daily. Under abnormal situations, such as severe diarrhea, it can be a major route of loss. In the absence of excessive sweating or diarrhea, the intake of sodium is reflected in the urinary output. Sodium balance can be obtained in 3 to 5 days after a constant sodium diet. It is estimated that the daily obligatory sodium losses are as follows: Urine 35 mg, stool 25 mg and skin 25 mg for a total of 85 mg. Providing normal conditions are present, the need for excessive intake of salt is, therefore, not justified.

There is abundant evidence relating salt to human hypertension. Ambard and Beaujard in 1904 first made the proposal that salt ingestion may lead to hypertension. Thereafter, Allen in 1920 and 1922 published extensive data incriminating salt in the development of hypertension. The first clinical therapeutic success of limiting sodium intake was reported by Kempner in the period of 1945 to 1950. He demonstrated the effectiveness of a rice-fruit diet in patients with malignant hypertension. However, by those who used this modality of treatment, the rice-fruit diet was a drastic change in a society accustomed to the salt appetite, which, in many instances, is best described as salt hunger or salt craving.

From the epidemiological standpoint there is also evidence that increased salt consumption is related to hypertension. For instance, there is a low prevalence of hypertension among Eskimos in Alaska, Marshall islanders in the Pacific and Yanomamo indians in the Brazil-Venezuela border. This seems to correlate very well their low intake of salt. In these civilizations the average daily intake of salt may go from 1 to 7 grams per day. In comparison, Japanese people consume an average of 14 to 26 grams per day. Their prevalence of hypertension is perhaps the highest in the world.

It has been possible to develop genetically predetermined hypertension in the rat by administration of salt early in life. This genetic vulnerability to salt may be ascribed to an inherent difficulty of the kidney in handling salt. It has been demonstrated that sodium transport is marked-

ly affected in this strain of hypertensive rats. Studies in our laboratories measuring the activity of the enzyme $\text{Na}^+ - \text{K}^+ - \text{ATPase}$, have disclosed an inhibitor of sodium transport. It appears that the excessive amounts of salt intake together with an inability of the kidneys to excrete sodium triggers the release of a transport inhibitor. This leads to a reduction of the transport of sodium in various organs, including blood vessels, which may result in a rise in blood pressure.

The advent of the thiazide diuretics in 1957 changed the whole spectrum of the treatment of hypertension even to the extent that they still constitute the first line drug in the antihypertensive armamentarium. The fact that it was difficult to maintain a person on a low salt diet to produce a significant drop in blood pressure fostered the use of diuretics, albeit that on chronic ingestion their mechanism to reduce blood pressure may not be related to natriuresis.

But why is it so difficult to maintain a low sodium intake? Some of the reasons that have been advanced to explain it are as follows: 1) palates are accustomed to salt since infancy and it can be distressing to avoid it, 2) diets are complex and may be expensive and 3) patients may be unaware of the salt content in processed foods or even common foods such as cheese or milk.

Several conclusions may be derived from the aforementioned facts:

- 1) Salt is consumed in a surreptitious manner in modern society.
- 2) Salt may produce or even aggravate hypertension.
- 3) Salt restriction is difficult and salt depleters are necessary to control or partly reverse the positive sodium balance.

Needless to say that hypertension is the most prevalent affliction of humanity and contributes to an increased cardiovascular morbidity and mortality. In these modern times physicians and their patients have worried much more about the ill effects of cigarette smoking, obesity, cholesterol, triglycerides and talc on rice than about their salt intake and its relationship to hypertension. It is time that a serious attempt be made to advocate the control of salt intake in the community.

In a recent survey of the Food and Drug Administration (FDA) it was clearly concluded that most common food additives are harmless but salt was targeted for restriction or possible removal from the food supply because of the potential of producing or aggravating hypertension. Sanford Miller, director of the FDA stated that the agency will expect a voluntary effort by food companies to restrict the addition of salt to their products. He ascertained that "it would be extraordinarily difficult to ban salt or to establish appropriate levels for each individual product, but we will if there is no voluntary effort".

The words of Sanford Miller should be welcomed by the medical community and it is up to physicians to stress the restriction of salt. Salt temperance should start in the pediatric age and thus accustom the palate to a low salt diet. It is known that young normotensive children of hypertensive parents constitute a high risk segment of the population and should be directed to avoid salty foods. It is foreseen that this dietary change will reduce the prevalence of hypertension seen later in adult life. The net result will be less cardiovascular mortality, a more productive life and containment of medical costs.

It would be good for modern society to go back to "uncivilized" ways of living by avoiding salt in the diet and thus preventing the catastrophic effects of hypertension.

SCREENING FOR INFECTION WITH
SCHISTOSOMA MANSONI IN PUERTO
RICO: A LIMITED SEROLOGIC SURVEY
UTILIZING THE CIRCUMOVAL
PRECIPITIN TEST

George V. Hillyer, PhD
Rosa Lluberes, MT
Carlos Ramírez Ronda, MD

Summary: Serum specimens were obtained from 196 individuals at the 1977 annual Health Fair held at the San Juan Coliseum. These individuals were residents of 19 cities and towns in Puerto Rico, although the majority came from three municipalities in or near metropolitan San Juan. All of the serum samples were tested two or more times for antibodies to *Schistosoma mansoni* eggs by the circumoval precipitin (COP) test. The percentage of subjects with positive COP reactions was 13.8 percent with an equal distribution among males and females; 16 percent of the subjects from the San Juan metropolitan area were positive. Although the sample was small the results suggest that infection with *S. mansoni* may be more widespread than is generally recognized. A review of some of the early literature related to human schistosomiasis in Puerto Rico is presented.

Introduction

Parasitologic proof of infection in man with *Schistosoma mansoni* is established by identifying eggs in fecal samples or by biopsy. In 1904 González Martínez demonstrated for the first time that *S. mansoni* was found in humans in Puerto Rico. His autopsy findings and stool examinations performed on patients in different areas of the Island as part of the Anemia Commission established that schistosomiasis was indeed prevalent in many areas of the island (1, 2). In a subsequent review (3) González Martínez reported that human schistosomiasis was present in the North, East, South and West areas of Puerto Rico and in the basins of the large rivers. With the exception of Utuado, there were no other endemic areas in the mountains. Using an insensitive thin smear, the Anemia Commission in 1904 only found 21 schistosome cases out of 5,000 anemia patients (0.4 percent). This may have been a reflection, however, of the fact that schistosome eggs had just been described for the first time in this part of the world. In 1913, investigators at the Institute of Tropical Medicine of Puerto Rico found 320 cases of schistosomiasis out of 10,140 patients (3.16 percent), again, using an insensitive thin smear fecal examination (3). Interestingly, one of the infected cases was "a patient coming from Santo Domingo." The report does not state where the infection was acquired.

Since the Anemia Commission report, seven large surveys for the prevalence of the Schisto-

From the Laboratory of Parasite Immunology, Dept. of Biology, University of P. R., Río Piedras, P. R. 00931, the General Medical Research Lab., Veterans Administration Center, and the Department of Medicine, UPR Medical Sciences Campus, San Juan, Puerto Rico.

Presented at annual meetings (1979) of the P. R. Chapter of the American College of Physicians and P. R. Medical Association.

Abstract published in Bol. Asoc. Med. P. R. 78: 236-237.

TABLE I

Chronology of Surveys for Prevalence of *S. Mansoni* Infection in Puerto Rico

Year	Investigators	Population Studied	Diagnostic Test	Comments
1927-28	Hoffman	635 All Ages	Single Thin Smear Fecal Exam	20 Percent Pos.
1934	Faust, et al	1,003	Fecal Concentration	12.2 Percent Pos.
1945	Weller and Dammin	19,139 Selective Service Registrants	Single Fecal Exam (1 gram)	9.9 Percent Pos.
1953	White, et al	8,955 Students	Single Fecal Exam (1 gram)	10.0 Percent Pos.
1963	Kagan, et al	10,824 Students 5th Grade	Skin Test	13.5 Percent Pos. Reactors
1969	Ruiz-Tiben, et al	9,365 Students 5th Grade	Skin Test	13.6 Percent Pos. Reactors
1976	Negrón and Nazario	10,224 Students 5th Grade	Skin Test	5.3 Percent Pos. Reactors

somiasis in Puerto Rico have been performed (Table I). Three of these involved stool examinations of varying sensitivity. Hoffman in 1927 used a fecal thin smear and investigated over 600 individuals of all ages from nine districts of Puerto Rico, and found infections in eight with an overall prevalence of 20 percent (4). Faust et al (5) examined 1,000 fecal samples from five regions (Río Piedras-Trujillo Alto, Caguas, Guayama, Utuado, Mayagüez) of Puerto Rico and found an overall prevalence rate of 12.2 percent. Weller and Dammin (6) surveyed during World War II 19,139 Selective Service registrants island-wide by examining 1 gram of feces and found a prevalence of near 10 percent. White et al (7) in 1953 examined 8,955 students in selected municipalities using a similar fecal concentration method and also found a prevalence of 10 percent. These results were in close agreement with the geographic distribution found by Weller and Dammin.

In 1963, 1969, and 1976 island-wide sur-

veys were conducted examining fifth-grade students using the intradermal test. In the 1963 study Kagan and collaborators found 13.5 percent positive skin reactors (8). Six years later Ruiz-Tiben et al also detected 13.6 positive skin reactors (9). In 1976, Negrón and Nazario performed a similar survey and reported only 6 percent positive skin reactors (10). One major problem in this last survey was that the skin test reactivity was "adjusted" downward because the 1976 antigen used elicited more intense skin reactivities than the stored and retested 1969 antigen. It should be stated that the criterion for positivity was slightly different in each of the three skin test surveys.

In a combined study 9 serologic tests were evaluated for the diagnosis of infection with *S. mansoni* in Puerto Rico (11-12). The standard for determining infection were 3-6 stool examinations using the sensitive and quantitative modified Ritchie

TABLE II

Distribution of Serum Samples Obtained in the 1977 Health Fair at the San Juan Coliseum
According to Residence of the Individual

Town	Number	No. Cop. Positive
Aguadilla	1	0
Arecibo	2	0
Bayamón	19	1
Caguas	3	1
Canóvanas	3	1
Carolina	23	1
Cataño	2	0
Cayey	1	1
Guaynabo	4	1
Hormigueros	2	0
Las Piedras	2	0
Luquillo	2	0
Mayaguez	2	0
Ponce	3	1
Río Grande	4	1
Río Piedras	68	12
San Juan	48	7
Toa Baja	3	0
Trujillo Alto	4	0
	196	27

formol-ether concentration (MRC) technique (13). In the study the circumoval precipitin (COP) test (originally described in 1954 by Oliver-González (14)) had the highest diagnostic sensitivity and specificity. The test was sensitive enough to detect antibodies in 8 (80 percent) of 10 infected individuals passing less than one *S. mansoni* egg per gram feces. After multiple (3-6) stool examinations 73 (60 percent) of 122 individuals were found infected with *S. mansoni*. With one COP test 69 (57 percent) of the 122 were correctly identified as infected while a single stool examination using the MRC technique detected 51 (42 percent). Thus a single COP test accurately identified more infected individuals than a single stool examination.

For the above reasons we decided to perform a limited survey to detect infection with *S. mansoni* by the COP test using the sera from individuals

collected at a local health fair.

Materials and Methods

At the 1977 Annual Health Fair held at the San Juan Municipal Coliseum 196 serum samples were obtained from volunteers who donated blood samples which were then tested for antibodies to diphtheria and tetanus. Although not part of the original study design, the numbered serum samples were then tested for *S. mansoni* antibodies the results of which are reported herein.

The individuals lived in 19 cities and towns in Puerto Rico although the vast majority of them lived in areas in or near metropolitan San Juan (Table II). All of the serum samples were tested two or more times for antibodies to *S. mansoni* eggs by the circumoval precipitin test (11, 12, 14) using fresh *S. mansoni* eggs obtained from the livers of infected mice. Serum and eggs were incubated at 37° C and read at 24 and 48 hours. Samples were considered posi-

TABLE III

Distribution of COP Test positivity by sex of individuals who donated a blood specimen during the 1977 Health Fair at the San Juan Coliseum

	Males	Females	Total
Positive	12	15	27
Negative	70	99	169
Total	82	114	196

TABLE IV

Distribution of COP test positivity by age among individuals who donated a blood specimen during the 1977 Health Fair at the San Juan Coliseum

AGE (years)	No. Positive	No. Negative	Total	Percent of Total	Percent of Total Positive
0 - 9	0	2	2	1	0
10 - 19	4	23	27	13.7	14.8
20 - 29	9	37	46	23.4	33
30 - 39	3	30	33	16.8	11
40 - 49	5	22	27	13.8	18.5
50 +	6	55	61	31	21.8

ve if the eggs contained globular blebs or septate precipitates. Percent eggs reactive in positive serum samples ranged from 3-47 percent. At least 100 mature eggs were examined for precipitates with each serum sample.

Results and Discussion

The reactivity of all serum samples tested is summarized in Table III. No differences between males and females are apparent. However it was surprising to see an overall rate of 13.8 percent positive reactors.

Most of the serum samples obtained were from individuals living in or near the San Juan metropolitan area. Of the 116 samples collected from

residents of San Juan and Río Piedras, 16.4 percent ($n=19$) were positive by the COP test. Of these, 93 percent of the reactions were blebs suggesting low levels of antibody. Although the sample size was small, this finding is of interest as it may be related to the movement of city dwellers to the country during weekends. In the present study most of the reactions had globular bleb precipitates suggesting low levels of antibody. The COP test is known to become negative following successful treatment (15).

The age group with highest positivity (33 percent) was that between 20 - 29 years of age, although this group comprised 23.47 percent of the sample total. This age-prevalence is quite similar to that reported in a prospective community-based study of *S. mansoni* infection in eastern Puerto Ri-

co (16). Those less than 20 years old (only 2 less than 10 years of age) comprised 14.7 percent of the sample total and had a similar percent in terms of total reactors. A summary of percent reactors by age is found in Table IV.

At present the true prevalence of infection with *S. mansoni* in Puerto Rico is unknown. Using a sensitive and specific serologic test such as the COP reaction, and with a limited number of samples, a surprising 13.8 percent reactors were obtained in this study, and most of the positives were in the 10-29 years old age group. Since chemotherapy for schistosomiasis has been virtually unavailable until recently (November, 1980) this seropositivity rate may be a fairly reliable index for the limited population examined.

In 1976, an island-wide skin test survey was done with 5th grade children (mostly 11 year olds) (10). In that survey the skin test antigen was more reactive than the one used in the 1969 survey and the authors "adjusted" the reactions downward, coming up with an overall positive reactor rate of 5.3 percent. However, in the age group tested, the skin test is known to have a low sensitivity. For example, Hiatt et al in 1978 skin tested children near Las Piedras, Puerto Rico and found only 36 percent reactors among those proven infected parasitologically (=sensitivity) (17). In 1973 in the Boquerón study population over 40 percent of the males and around 16 percent of the females 14 years of age or younger were proven infected with *S. mansoni*. Since chemotherapy was not used in the study population, the prevalence rate should have remained the same through 1976. However, the 1976 skin test survey (after adjustment) showed a reactor rate of only 11.6 percent in the fifth grade school-children in the areas of Gurabo, Juncos, and Las Piedras. Based on the discussion above, the 1976 skin test results should be considered as being on the conservative side.

These studies suggest that schistosomiasis is still with us in Puerto Rico but that the true infection status is unclear. With the recent availability of chemotherapeutic agents for schistosomiasis a true prevalence figure will be even more difficult to obtain although prevalence should be expected to decline. However, our results point toward the im-

mediate need for a large and accurate parasitologic or serologic survey to define the status of schistosomiasis in Puerto Rico.

Acknowledgments

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related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000, 25 mg. (peach) in bottles of 100 and 1000, unit-dose blister packs, boxes of 100 (10 x 10 strips).

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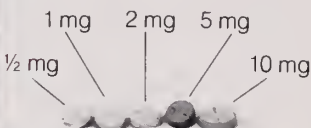
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midal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn.

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IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

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MITRAL VALVE COMMISSUROTOMY BY JOHN ALEXANDER: REPEAT SURGERY 28 YEARS LATER

Jorge O. Just Viera, MD

Abstract: A closed mitral valve commissurotomy in a 22 year old man by Dr. John Alexander three years before his death was successful for 28 years. The patient underwent uneventful repeat commissurotomy and valvuloplasty. Dr. John Alexander contributed to thoracic surgery and to surgical education. The excellent results he obtained in this very ill cardiac patient is a tribute to this surgeon who participated in the developing field of cardiac surgery despite his illness.

Introduction

Dr. John Alexander is famous for his contributions to the development of the specialty of thoracic surgery. His classic works on the surgical treatment of tuberculosis are a landmark (1, 2). Less known, however, is his participation in the early days of cardiac surgery. A patient was operated upon by Dr. Alexander in 1951 for mitral stenosis. Restenosis of the valve occurred and the patient had successful repeat mitral valve surgery 28 years later.

Case Report

E. W., Unit No. 167714-5, a 50-year old white male, was referred for heart surgery on February 17, 1979, with arrhythmias and shortness of breath to the Cardiovascular Center, Mercy Hospital, Benton Harbor, Michigan. Closed mitral commissurotomy was performed by John Alexander in 1951 for mitral stenosis in Ann Arbor. The patient was then a fairly ill 22 year old and was referred there by Dr. John Manning, from St. Joseph, Michigan. When first seen in Ann Arbor in June 1951 he complained of paroxysmal nocturnal dyspnea and dyspnea on exertion. On examination, the point of maximal cardiac impulse was at the fifth intercostal space, nine centimeters from the midsternal line. A palpable thrill and a low pitched diastolic murmur were found, with a loud, snapping first sound at the apex. The second sound was split. The electrocardiogram was compatible with the presence of mitral stenosis.

On October 29, 1951, the patient was taken to the operating room according to the operative note, corrected and signed by Dr. John Alexander. He was the surgeon, and the assistants were Dr. Herbert Sloan and Dr. Gardner. Anesthesia was induced with cyclopropane oxygen combination and continued with ether vapor and oxygen. The chest incision was made slightly below the fourth rib with the patient in the right lateral position. The fourth rib and about half of its cartilage were resected to the posterior axillary line. The anterior portion of the left auricle and the appendage were enlarged. The pericardium was incised vertically 1.2 cm anterior to the phrenic nerve and horizontal extension increased exposure. The regularity of the heart was maintained through most of the operation by intravenous 0.5 per cent procaine solution in glucose. From time to time several drops of 5 percent procaine solution were placed upon the epicardium.

From St. Joseph Mercy Hospital, 900 Woodward Avenue, Pontiac, Michigan 48053.

The auricular appendage was clamped and a heavy silk purse string was placed. A more superficial purse string was also placed in such a position that Dr. Sloan, the assistant, could control them. The special auricular clamp was then placed and the appendage opened. The finger was introduced with control of the purse strings by traction. When the finger was advanced to the valve orifice, there was no palpable evidence of regurgitation. The diameter was calculated to be 1 cm. At the time the orifice of the mitral valve was estimated, the heart became irregular and underwent a long diastole because "the finger was held there too long." It was then withdrawn and the heart quickly recovered its normal rhythm. At one point, however, the finger slipped beyond the distal purse string and about 250 cc of blood were lost, which was considered "advantageous, rather than otherwise," because of the pulmonary congestion. The finger was introduced without further loss of blood and was advanced to the orifice and by firm pressure passed through the orifice by tearing of the lateral commissures. In order to enlarge the orifice still more, several jerky movements of the finger were made anterolaterally while the cardiac wall was supported opposite the lateral commissure with two fingers and enlarged the orifice approximately to the mitral ring. The resulting diameter of the orifice appeared to be about 1.5 or 1.75 finger breadths. The dilating finger was gradually withdrawn and the deeper string was tightened. The auricular clamp was reapplied and the distal purse string tightened as the finger was completely withdrawn. Repair of the auricular incision and the pericardial incision were performed. The chest wall was closed after the instillation of 50,000 units of penicillin and one gram of streptomycin in the pleural cavity while 100,000 units of penicillin were placed in the pericardial cavity. The blood loss was 1206 cc.

The patient did very well postoperatively. His surgeon and his surgery permitted his return to work and to a productive life until October 1977 when shortness of breath caused admission to the hospital. An electrocardiogram showed paroxysmal atrial tachycardia. An echocardiogram revealed moderate to severe mitral stenosis. Cardiac catheterization was performed. The pulmonary arterial pressure was normal. The left atrial pressure was elevated and the atrioventricular pressure gradient was approximately 10 mm Hg, suggesting moderately severe mitral stenosis. Coronary angiogram showed normal right and left arteries. Digitalis was prescribed, but because the patient felt that his symptoms were increasing and he recognized the same fatigue that he had in 1951, he requested surgery.

On February 19, 1979, a midline sternotomy was performed. The pericardium was densely adherent to the myocardium and was separated from it by sharp dissection. The heart was moderately enlarged but contracted well. After uneventful cannulation and heparinization, the patient was placed on cardiopulmonary bypass and was cooled to 28°C. The aorta was clamped and the left atrium was opened. There were no clots in the left atrium. The valve was

inspected. The antero-septal commissure was fused mainly at the leaflet level, whereas the posterolateral commissure also had underlying chordal fusion and shortening. Commissurotomy was performed anteriorly first through the well defined valve margins. Good chordal support was present. The valve was opened anteriorly for about 1 cm. Posteriorly the valve was also opened to the annulus to preserve chordal support. The posterior papillary muscle was then incised lengthwise about 1.5 cm. The heart was defibrillated, and with the heart beating, competency of the valve was tested by direct inspection of the valve. There was minimal insufficiency through the posterior commissure and this was corrected with an annuloplasty suture placed in the posterior angle. Retesting of the repair on several occasions revealed no insufficiency. The atrium was then closed.

The patient did quite well postoperatively. He did not have any systolic murmur. Atrial fibrillation was initially treated with digitalis and then by cardioversion. Normal sinus rhythm returned. Coumadin and digitalis were prescribed, the patient was discharged in good condition and has done extremely well since. He returned to work in 8 weeks.

Discussion

The numerous contributions to thoracic surgery by John Alexander include the development of educational programs for training thoracic surgeons at the University of Michigan. The operative report from Ann Arbor was two pages long and included 22 corrections by Dr. Alexander. Some were for grammatical errors, all of which reflect his attentiveness to the task.

The long-term results of open mitral valvuloplasty at the University of Michigan were reported by Byrne, et al (3). Fourteen of the 51 reported patients had had previous closed mitral commissurotomy. Mitral valve replacement was required in six patients up to 12 years following open valvuloplasty in this group. Nathaniels and co-workers reported a 15-year followup of 100 patients with closed mitral valvuloplasty (4). Twenty-seven patients had undergone no secondary procedure to the mitral valve at 15 years. Patients who required a second valvuloplasty did so at an average interval of eight years. Repeat valvuloplasty in our patient can provide beneficial long-term results and postpone the need for mitral valve prosthesis.

The purpose of this report, however, is to

pay tribute to Dr. John Alexander. Despite his illness and notwithstanding his justified fame in pulmonary surgery, he chose to participate in cardiac surgery, a developing field at the time. Possibly, this was the only cardiac procedure done by him (5). Nonetheless, he capably relieved incapacitating mitral valve obstruction for 28 years in a patient who remained grateful to him.

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EFFECT OF ESTROGEN ON THE VAGINAL CYCLICITY OF NEONATALLY ANDROGENIZED RATS

F. González Lima, PhD

Resumen: Para aclarar la relación entre la influencia hormonal pospuberal y la androgenización neonatal, en la presente investigación se examinó el efecto de inyecciones de 20 µg de benzoato de estradiol (EB) en la desaparición del ciclo vaginal de ratas tratadas neonatalmente con propionato de testosterona (TP). La llegada de la esterilidad se identificó por el patrón vaginal de estrus persistente (PVE). Una inyección de EB indujo una pseudopreñez consistente de 10-11 días con un patrón vaginal de diestrus constante en las ratas androgenizadas. Las inyecciones de EB tuvieron un efecto inhibitorio sobre la incidencia de PVE en ratas tratadas con TP. Se sugiere que el estrógeno induce una modificación subsiguiente en el cerebro androgenizado neonatalmente que es mediada por un aumento de prolactina y una disminución asociada en la actividad hipotalámica. Se sugiere, además, que esta modificación retrasaría la velocidad del envejecimiento somático en ratas jóvenes androgenizadas en términos del patrón PVE.

Summary: To further clarify the relationship of postpuberal hormonal feedback and neonatal androgenization, the present research examined the effect of injections of 20 µg estradiol benzoate (EB) on the onset of vaginal acyclicity in rats treated with testosterone propionate (TP) as neonates. Persistent vaginal estrus (PVE) smears were used to indicate the onset of sterility. Pseudopregnancy induced by a single EB injection consisted of 10-11 days of cons-

tant diestrus smears in androgenized females. EB injections had an inhibitory effect on the incidence of PVE in TP-treated female rats. It is suggested that estrogen induces a subsequent modification of the neonatally androgenized brain that is mediated by elevated prolactin release and correlated decrease in hypothalamic activity. It is further suggested that this modification could retard the rate of somatic aging in young androgenized rats as measured by the PVE pattern.

Introduction

Testosterone propionate (TP) injected prior to the fifth day of age in amounts larger than 50 µg causes female rats to become sterile and anovulatory. With such large dosages no cyclicity is seen at puberty and the female rat is immediately sterile. However, smaller dosages of TP produce animals which cycle, the cycles lasting longer the smaller the dosage of TP. The age at which the androgenized female rat stops showing cycles and normal reproductive functioning is a function of the dosage of androgen injected (1).

This phenomenon was first described by Swanson & van der Werff ten Bosch (2) who found that female rats of 70 days of age given 5 µg TP when 5 days old had ovaries similar to those in normal animals. By 150 days of age, however, the ovaries in the treated rats were polyfollicular and with no corpora lutea. This indicates that female rats injected with a minimal dose of androgen as neonates show normal ovulatory capacity for a period of time after puberty before the onset of sterility. This phenomenon was named the delayed anovulatory syndrome (DAS) by Gorski (1).

While determined by dosage of neonatal an-

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drogen, the timing of the onset of sterility is also influenced by postpuberal factors. It has been suggested that low dosages of androgen given to the neonatal female rat may affect a developmental process and promote the premature aging of the central nervous system (2). It also has been suggested that the anovulatory syndrome and subsequent modification of the central nervous system is produced by postpuberal ovarian secretions which interact with neonatal androgen to accelerate the loss of normal function (1).

Evidence that the presence of ovarian secretions accelerate the onset of sterility has been provided by Arai (3). In his study female rats were given minimal doses of TP neonatally and ovariectomized at either 60 or 90 days of age. When they were 140 days of age, all females received ovarian grafts. Females ovariectomized at 60 days cycled longer than those with ovaries until 90 days of age. Arai interprets his data as indicating that the development of the delayed anovulatory syndrome (DAS) is dependent on postpuberal ovarian feedback secretions. However, employing similar methodologies, other researchers report that ovarian secretions do not accelerate the onset of sterility (4). Other findings also seem inconsistent with the view that ovarian feedback supplements the effects of neonatal androgen (5).

To further specify the relationship of postpuberal ovarian feedback and neonatal androgenization, the present research examined the effect of injections of estradiol on the onset of vaginal acyclicity in rats treated with testosterone as neonates.

Materials and Methods

Female rats of the Sprague-Dawley strain were maintained in an air-conditioned room on a 12 hr. light - 12 hr. dark inverted illumination schedule. By three days of age, litters were adjusted to 10 individuals by discarding or fostering extra male pups. At this time, half of the female pups in each litter were randomly assigned to receive injections of either 1.5 μ g testosterone propionate (TP) in .05 cc sesame oil or sesame oil alone to form the TP-treated and the oil-treated groups. Individual body weight was recorded prior to the injection.

By 28 days of age, the animals were weaned and then lived three to a cage with Purina Rat chow and water available *ad libitum*. Within the two neonatal treatments, subjects were randomly assigned to one of two treatments. An outline of the experimental design and the number of subjects in each group is provided in Table I. By 10 weeks of age, female rats from groups 3 and 4 were injected with 20 μ g estradiol benzoate (EB). Injections were given intramuscularly about three hours before the onset of the light portion of the light-dark cycle. A second series of 20 μ g EB injections were given when the animals were returning to normal cyclicity.

Vaginal smears were obtained daily after the first injection of estrogen. Finally, the oil-treated control animals (Group 2) were smeared for a period of about three weeks at the end of the study. Flushing of the vagina with deionized water and toluidine blue stain were used for preparing the smears. Then smears were microscopically examined and classified as proestrus (P), estrus (E), metestrus (M), or diestrus (D). Persistent vaginal estrus (PVE), defined as eight consecutive days of E smears or nine days of E out of ten, and constant diestrus (CD) smears were used to indicate the onset of sterility.

Results

Female rats injected with 1.5 μ g testosterone propionate (TP) as neonates showed a period of normal vaginal cyclicity before developing smears of persistent cornification or diestrus cells. Table I shows the effect of estradiol (EB) injections on the percentage of rats reaching persistent vaginal estrus (PVE) smears by 150 days of age. By this age, all of the animals treated with only TP showed non-cyclic PVE patterns (Group I). But only 57.1 percent of the TP-treated animals injected with EB showed PVE patterns (Group 3). A chi-square test of these data revealed a statistically significant difference between the proportion of PVE animals in groups 1 and 3, $X^2 = 5.663$, $p < 0.02$. Therefore, estradiol injections had an inhibitory effect on the incidence of PVE in TP-treated female rats.

Two androgenized females treated with EB developed a vaginal pattern of constant diestrus (CD) smears rather than persistent estrus smears. Table II presents the duration of induced pseudopregnancy, as measured by number of days of diestrus va-

TABLE I

Effect of estradiol injections on the percentage of subjects reaching persistent vaginal estrus (PVE) smears by 150 days of age

Group	Treatment		No. Rats	Incidence of sterility (Percent PVE)
	Neonatal	Adult		
1	Testosterone Propionate	Sesame Oil	11	100
2	Sesame Oil	Sesame Oil	11	0
3	Testosterone Propionate	Estradiol Benzoate	7	57.1 *
4	Sesame Oil	Estradiol	8	0

* Significantly different from Group 1, $p < 0.02$

TABLE II

Effect of two injections of 20 µg of estradiol benzoate (EB) on the vaginal cyclicity of androgenized female rats (Group 3)

Day of cycle injected	No. of Diestrous smears after 1st injection	No. of Diestrous smears after 2nd injection *	Total No. of days with Diestrous smears	Quality of cycles after the end of 2nd pp	Age of PVE (Days)
PE	11	10	21	Poor	118
PE	11	11	22	Good	> 145
E	12	7	19	CD**	---
E	11	13	24	PVE	114
E	12	13	25	CD**	----
E	2	1	3	PVE	103
M	11	12	23	Poor	129
Mean:	10	11	20		> 122

* Second injections were given during E or M in the rats first injected on PE, and during P or PE for the first injected on E or M

** Constant diestrus

TABLE III

Effect of two injections of 20 ug of estradiol benzoate on the vaginal cyclicity of
normal female rats (Control Group 4)

Day of Cycle injected	No. of Diestrous smears after 1st injection	No. of Diestrous smears after 2nd injection *	Total no. of days with Diestrous smears	Quality of cycles after the end of 2nd PP
P	8	9	17	Fair
P	4	10	14	Fair
E	7	11	18	Good
E	11	11	22	Poor
E	8	5	13	Good
E	4	9	13	Fair
E	11	11	22	Fair
M	18	6	24	Good
Mean:	9	9	18	

* Second injections were given during E or M to the rats first injected on P, and during P or PE for the rats first injected on E or M

ginal smears, in the TP-treated females. Average duration of pseudopregnancy was 10-11 days after a single EB injection. In pseudopregnant androgenized animals, the quality of estrus cycles after the end of the second pseudopregnancy was poor and irregular. Identically EB-injected control animals, shown in Table III, showed primarily regular cycles after pseudopregnancy. The average total duration of constant diestrus smears in control animals was 18 days as compared to 20 days in TP-treated animals.

During the period of reproductive capacity the androgenized females and the control females appeared to have the same functions. For example, behaviors such as locomotor activity, eating and drinking were found to be normal for the cycling androgenized females. Vaginal smears of the oil-treated control animals were examined daily during the last three weeks of the study and all females were cycling normally.

Discussion

The results indicate that uninterrupted cy-

cling of the ovarian-pituitary-hypothalamus system accelerated its offset of normal function in virgin androgenized females relative to those maintained pseudopregnant with injections of estradiol.

It has been suggested that neonatal androgen might accelerate the premature aging of an unknown system necessary for ovulation (2). This hypothesis maintains that neonatal treatment with testosterone propionate (TP) starts changes in the central nervous system which may require many weeks for complete expression, suggesting in this way that TP affects a developmental process. Our findings indicate that the action of neonatal androgen is not limited to its effect on a developmental process but it is influenced by postpuberal factors affected by estrogen administration.

Gorski (6) suggested that the influence of low doses of androgen is incomplete, and functioning parts of the ovulatory system can still support ovulation after puberty. This functional capacity is gradually lost and the delayed anovulatory syndrome (DAS) develops as a result of an independent modification of the neonatally partially differentiated nervous system (1). Our results support the idea

that hormonal feedback, independent of the direct action of androgen on the neonatal brain, are responsible for the DAS (3).

Our findings indicate that induced pseudopregnancy retards the course or rate of biological aging in young androgenized rats as measured by the PVE pattern. Most old normal females exhibit PVE as the initial event in senescence. These findings are in agreement with Arvey (7) who found that multiparous females had somatic characteristics that appeared younger and had a longer life-span than those which did not participate in reproductive processes in the course of their lives.

Gorski (6) and Arai (3) have offered an explanation for the independent modification that results in the delayed anovulatory syndrome in androgenized females. Arai (3) provides evidence suggesting that this modification is produced by postpuberal ovarian steroid feedback. He found that rats injected neonatally with 10 µg TP, which were ovariectomized at wither 60 or 90 days of age, when given ovarian grafts at 90 or 140 days of age, had cyclic ovaries whereas androgenized females with ovaries not removed were PVE when they were 140 days old. Arai concludes that the development of the DAS is dependent on the presence of ovarian secretions. Accordingly, if ovarian cyclic secretions could be reduced during adulthood, the age of the DAS should be delayed.

The present experiment seems to support this hypothesis because during estrogen-induced pseudopregnancy there are no cyclic ovarian secretions. This physiological sterility resulted in a delay on the onset of PVE comparable to what was predicted from the findings of Arai (3). However, there is no direct evidence that the modification responsible for the onset of sterility is produced by the ovarian steroid feedback. During pseudopregnancy changes occur in the entire neuroendocrine system. Therefore it is questionable as to what causal importance could be assigned to the many factors involved in estrogen-induced pseudopregnancy.

Hendricks et al (4) have attempted to specify the interrelationship of neonatal androgenization and postpuberal ovarian feedback. They report that ovarian secretions do not accelerate the onset of sterility and provide data which showed no

effect of either endogenous or exogenous ovarian hormones in the rate of the DAS. Furthermore, if the influence of ovarian steroids is responsible for the accelerated onset of sterility in the cycling females, then estrogen circulating postpuberally may be expected to complete the neural modification initiated by neonatal androgen. Conversely, deficit of the endogenous ovarian estrogen resulting from castration would be expected to have similar effects with the physiologically induced sterility resulting from pseudopregnancy. On the contrary, Arvey (7) reports that castrated females (low estrogen levels) appeared younger than controls during the reproductive period, but later in life castrated females appeared to be the oldest. This opposite aging effect of levels of estrogen during pseudopregnancy and castration indicates that the aging effect involved in the DAS is not due directly to estrogen levels but to a different mechanism.

Data from Napoli & Gerall (5) seem inconsistent with the view that ovarian feedback supplement the effects of neonatal TP on the onset of sterility. They found that the prepuberal administration of estradiol benzoate (EB) or the anti-estrogen MER-25 did not influence the percentage of minimally androgenized females exhibiting PVE when measured against time of vaginal opening. Estrogen given before puberty increased the number of TP-treated females showing PVE at each age examined over that obtained with Oil-treated androgenized females. But estrogen given prepuberally also induced precocious puberty. As Gerall (8) has argued, this initial aging effect produced by estrogen merely started sooner the endogenous timing of the DAS processes and, hence, the period of normal cyclic activity also ends sooner than in androgenized females given oil prepuberally.

During pregnancy and pseudopregnancy there are significant increases in ovarian progesterone levels. It can be argued that this hormone is responsible for the effects of pseudopregnancy on the DAS. However, 10 µg of progesterone administered daily for 16 to 18 days has been found to have no influence on the rate of biological aging in normal adult female rats (9).

Studies by Gorski (6) support the view that androgen may masculinize the brain by an action at

a very fundamental level of neuronal activity in the hypothalamus. His data support the view that androgen alters a fundamental neurochemical process, perhaps protein synthesis, decreasing hypothalamic activity in some way that prevents the cyclic release of gonadotrophic hormones. Clayton et al (10) have reported that three hours after TP administration RNA synthesis throughout the brain of the two-day-old female rat is significantly decreased. Since a decrease in hypothalamic activity is the initial event which produces premature aging in the neonatally androgenized female, the study of hormones related to decreased neuronal activity that are present during pseudopregnancy may indicate or explain to some extent the observed changes in the rate of the DAS and the nature of the secondary sterilization processes involved in the onset of sterility. Such discussion has been given elsewhere (11) regarding the role of prolactin in physiological sterility and aging processes during reproductive function in androgenized female rats.

Previous experiments by this author indicate that participation in reproductive processes such as pregnancy and lactation retard the rate of somatic aging in young neonatally androgenized female rats as measured by the PVE pattern (12, 13). In other words, anticipated "sterility" induced during normal reproductive states retards the function of the overall aging processes later in life. Similarly, as indicated by the present results, induced noncyclicity during pseudopregnancy retarded the subsequent onset of sterility (PVE) in androgenized females. It can be inferred that common mechanisms responsible for sterility during pseudopregnancy or reproductive states are also responsible for the modified rate of onset of sterility.

Particular attention must be paid to pituitary or hypothalamic hormones involved in physiological sterility during pseudopregnancy, pregnancy and lactation, all of which retarded the DAS (14). For example, Dan and Voogt (15) demonstrated that prolactin is the major luteotrophic hormone in the pseudopregnant rat. They concluded that daily surges of prolactin play an essential role in maintaining pseudopregnancy in the rat; and that the stimulation of luteinizing hormone (LH) secretion, which

leads to ovulation at the termination of pseudopregnancy, may be the result of a direct neural action of prolactin on the LH release mechanism. A similar critical controlling role of prolactin on reproductive biology has been recently specified during pregnancy and lactation (16, 17).

Early studies indicate that estradiol can deplete the hypothalamus of prolactin-inhibiting factor (PIF), thereby removing neural inhibition to pituitary prolactin release (18). In fact, a dose of 5 µg of estradiol benzoate produces a 10-fold increase in serum prolactin concentration (20). In the present experiment two injections of 20 µg EB reduced the incidence of vaginal PVE in androgenized rats, similar to the effects of pregnancy and lactation (12, 14). Since during pseudopregnancy, pregnancy, lactation and senile sterility (29) there are increased levels of prolactin and decreased levels of LH, our assumption is that these common neuroendocrine processes are involved in the aging of systems mediating reproductive function. These same processes are presumably responsible for the secondary sterilization of neonatally androgenized female rats. Consequently, the DAS may develop due to a subsequent modification of the partially differentiated hypothalamic-pituitary axis. This modification may be due to elevated prolactin release and correlated decrease in hypothalamic activity which may result in the physiological sterility mediating reproductive function.

If one accepts the assumption that the DAS represents a fair model for understanding reproductive aging in the female rat, the data discussed above are suggestive of a more generalized model of mammalian aging complementary to ovarian secretions (12). Details of the mechanism involved in the DAS and the validity of our interpretation await further research.

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COMMON OCULAR DISEASES IN CHILDREN

René Vázquez Botet, MD

SUMMARY: Examination of the eye should be a routine part of the periodic pediatric examination. The child should be examined by an ophthalmologist whenever a significant ocular abnormality or vision defect is noted. Any variation from normal development early in life may result in lifelong patterns of defective vision or abnormal ocular alignment. Early detection and treatment of strabismus in children is of primary importance; and proper assessment and management require a working knowledge of the various clinical types of strabismus, the method of detection, and the principles of treatment.

RESUMEN: El examen oftalmológico debe ser parte integral del examen pediátrico. El niño debe ser examinado por un oftalmólogo cuando se sospeche una anomalía ocular o un defecto en visión. Cualquier variación del desarrollo normal temprano en la vida puede resultar en patrones de visión defectuosa o anomalías en el alineamiento de los ojos para el resto de la vida. La detección y el tratamiento del estrabismo en los niños es de primera importancia; y el diagnóstico y manejo requieren un conocimiento de los varios tipos de estrabismo, los métodos de detección y las distintas formas de tratamiento.

Examination of the Eye

Examination of the eye should be a routine part of the periodic pediatric assessment. Screening in school and community programs can also be effective in detecting problems early. The child should be examined by an ophthalmologist whenever a significant ocular abnormality or vision defect is noted. Ideally, every child should have a thorough ophthalmologic examination by the age of 4 to 5 years. These are the crucial years for the detection and treatment of amblyopia, strabismus, high refractive errors, and certain tumors of childhood.

Basic examination, whether done by the pediatrician or ophthalmologist, must include evaluation of visual acuity and the visual fields, assessment of the pupils, ocular motility and alignment, a general external examination, and ophthalmoscopic examination of the media and fundi.

Visual acuity is best measured by the standard Snellen chart and this method should be used as early as the child's ability to name, copy, or match letter, symbols or number will allow. The "E" test, consisting of rows of the letter E in various sizes and directions, can also be used; children are asked to indicate the direction of the selected E by pointing their hands or fingers up, down, right or left.

Abnormalities of Refraction

Hyperopia — If parallel rays of light come to focus posterior to the retina with the eye in a state of rest (nonaccommodating), hyperopia or far-

HYPEROPIA

HYPEROPIA EXISTS WHEN PARALLEL RAYS OF LIGHT COME TO FOCUS POSTERIOR TO THE RETINA WITH THE EYE IN A STATE OF REST (NON-ACCOMMODATING).

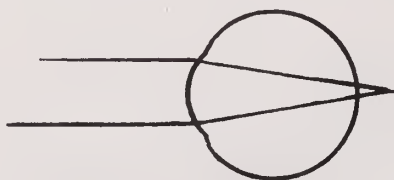


Figure 1: Hyperopia

sightedness exists (Fig. 1).

In hyperopia, accommodation is used to bring objects into focus for both distance and nearness. If the accommodative effort required is not too great, the child will have clear vision and will be comfortable for distance and close work. In high degrees of hyperopia requiring greater accommodative effort, vision may be blurred, and the child may complain of "eye strain", headaches, or fatigue. There may be associated esotropia (convergent strabismus, accommodative esotropia). Convex lenses (spectacles) of sufficient strength to provide clear vision and comfort are prescribed when indicated.

Myopia — In myopia, parallel rays of light come to focus anterior to the retina (Fig. 2). The principal symptom is blurred vision for distant objects. Myopic children tend to hold objects and reading matter close, prefer to be close to the blackboard, and may show disinterest in distant activities. Frowning and squinting are common since the visual acuity is improved when the lid aperture is reduced; the effect is similar to that achieved by closing or "stopping down" the aperture of the diaphragm of a camera.

Concave lenses of appropriate strength to provide clear vision and comfort are prescribed. Yearly re-evaluation is advised; simple myopia tends to increase through adolescence.

Amblyopia — This term refers to subnor-

MYOPIA

MYOPIA EXISTS WHEN PARALLEL RAYS OF LIGHT COME TO FOCUS ANTERIOR TO THE RETINA WITH THE EYE IN A STATE OF REST (NON-ACCOMMODATING)

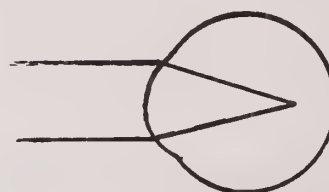
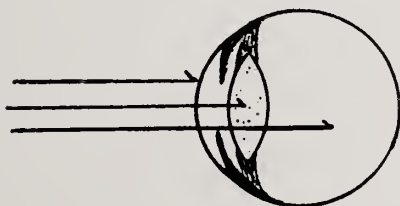


Figure 2: Myopia

mal visual acuity in one or both eyes despite appropriate correction of any significant refractive error. The impairment may be organic or functional. In organic types of amblyopia, the vision defect can be adequately explained by a pathologic change affecting the visual pathways. In the functional types of amblyopia, there is no such underlying pathologic alteration of the retina or visual pathways; rather, the impairment of vision is attributed to deprivation of sensory stimulation (disuse) or to inhibition (misuse). The most common cause of functional amblyopia is strabismus, in which amblyopia results from the lack of use or active suppression of macular vision in the deviating eye. Another common cause of functional amblyopia is uncorrected anisometropia; in this situation, the eye with the clearer retinal image is preferred for definitive seeing and the eye with the more blurred retinal image becomes amblyopic owing to a certain degree of sensory deprivation or inhibition. Similarly, corneal opacities and cataracts of childhood often lead to amblyopia of sensory deprivation (Fig. 3).

In nonorganic amblyopia, the severity of the defect in vision and the degree of reversibility of the condition depend on the age the impairment of function comes on, the duration of the impairment, and the age at which appropriate treatment is begun. It has been clearly demonstrated that the earlier the onset of the interference with visual func-

STIMULUS DEPRIVATION AMBLYOPIA



Anything that interferes with formation of a clear retinal image.

Figure 3: Amblyopia

HETEROPHORIAS AND HETEROTROPIAS

- TYPES -

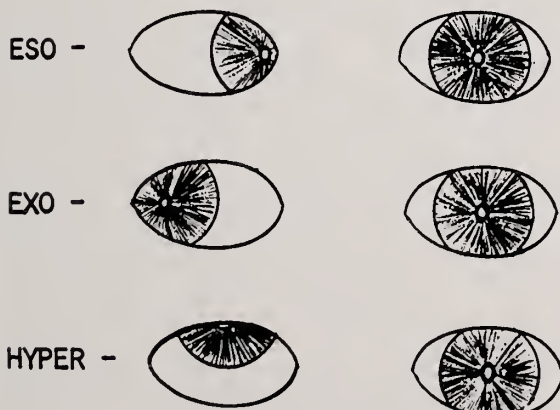


Figure 4: Classification of strabismus according to the direction of the deviation.

tion and the longer the duration of impairment, the more profound and irreversible will be the defect in vision.

In an infant, amblyopia can often be reversed in a matter of days or weeks. In an older child with longstanding amblyopia, months or years of treatment may be necessary.

Treatment of functional amblyopia involves (1) providing the clearest possible retinal image (for example, by correction of refractive error, removal of cataract), and (2) stimulation of forced use of the amblyopic eye. The preferred method of treatment is occlusion therapy, often referred to as "patching"; the better eye is simply covered to force use of the amblyopic eye.

Strabismus

Terminology — The two principal types of deviation or malalignment of the eyes are heterophoria and heterotropia. Heterophoria is a latent tendency to malalignment; the eye deviates only under certain conditions, such as fatigue, illness, stress, or dissociative testing, that interfere with maintenance of normal fusion. When control of the deviation exceeds the amplitude of fusion so that the deviation becomes manifest, the malalignment is termed heterotropia or simply tropia. The condition may be monocular or alternating, depending on the vision and fixation pattern. In alternating strabismus, either eye may be used for fixation or definitive seeing while the fellow eye deviates; since each eye is being used in turn, vision develops more or less equally in both. When only one eye is used (or preferred) for fixation and the fellow eye consistently deviates, the deviation may be referred to as monocular strabismus, or as a right or left strabismus; in this situation the child is prone to amblyopia or defective central vision in the deviating eye, as the result of disuse or misuse.

Strabismus is further described according to the direction of the deviation. Convergent deviation, a crossing or turning in of the eyes, is designated by the prefix *eso-* (hence esotropia, esophoria), while a divergent deviation or turning outward of the eyes (commonly referred to as wall-eye) is designated by the prefix *exo-*. Vertical deviations are indicated by the prefix *hyper-* (Fig. 4).

Methods of Testing for Strabismus — A sim-

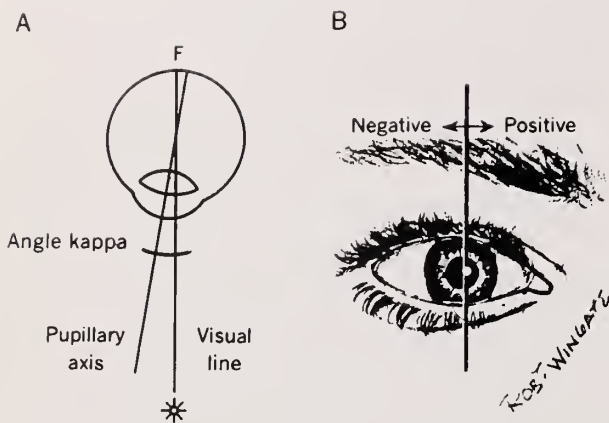


Figure 5: Hirschberg Test

ple and reliable technique for assessing the alignment of the eyes in children is the Hirschberg or corneal light reflex test (Fig. 5). The Hirschberg test involves simply observing the position of the corneal reflexes (reflections) when a small focal light is directed toward the patient's face. If the light reflex is well centered in each eye, the eyes are properly aligned. If the light reflex in one eye is well centered while the light reflex in the fellow eye falls nasally or temporally, superiorly or inferiorly, a deviation exists (Fig. 6). The amount of prism needed to re-center the light reflex in the deviating eye gives an accurate measurement of the degree of deviation.

Before proceeding with the light reflex, it is advisable to take time to simply observe the child at a nonthreatening distance in quiet, pleasant surroundings while the child plays or sits comfortably with a parent; this is particularly important with the very young, or with the shy, fearful or retarded child.

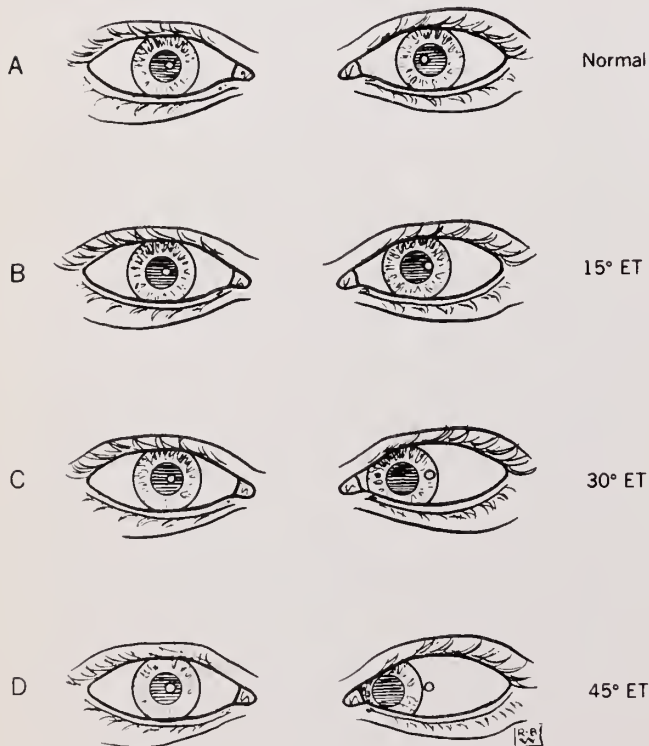


Figure 6: CORNEAL LIGHT REFLEXES
A — Normal position B, C and D — Light reflex is displaced temporally (Esotropia).

Common Types of Strabismus

I Non Paralytic

Esotropia — Congenital and Accommodative

Exotropia

II Paralytic

3th, 4th, 6th nerve palsy

I Non Paralytic Strabismus

Congenital Esotropia

Congenital esotropia is characterized by a large inward deviation of one or either eye prior to six months of age (Fig. 7). The refractive error is



Figure 7: Congenital Esotropia — Right eye is deviated in.

usually small and about 40 percent of the patients have amblyopia.

Treatment consists of treating the amblyopia if present and surgery to straighten the eyes. Bilateral medial rectus recession is the procedure of choice. Better long term eye stability is achieved if the eyes are aligned before the second year of life. Although a definite diagnosis of congenital esotropia is not made until six months of age which is the first time the eyes "work" together, a complete eye examination should be done at any time an esotropia is suspected since Retinoblastoma, tumor of retinal origin, can present as strabismus.

True congenital esotropia must be differentiated from the false impression of deviation created by certain anatomic variations. Children with prominent epicanthal folds and broad, flat nasal bridges will often appear cross-eyed when they in fact have their eyes straight; this is pseudo-strabismus. In these cases the corneal light reflex is well centered in each eye (Fig. 9).

Accommodative Esotropia

This type of deviation most commonly appears at 2 to 3 years of age, with a range of onset from



Figure 8: External photo of Retinoblastoma.

6 months to 8 years of age. The majority of the affected children have high hyperopia. In order to bring in focus the images, the child has to accommodate the amount of hyperopia present. Any time accommodation is exerted convergence also occurs (synkinetic near reflex). Some patients can not handle the excessive convergence that occurs with the high degree of accommodation required to see the images clearly and deviate one eye. At first the deviation may be intermittent. Amblyopia is frequent. In some cases there is also a disturbance of the distance — near relationship so that the amount of crossing at near gaze is greater than that for distance (Fi-



Figure 9: Pseudostrabismus — Wide nasal bridge and corneal light reflex centered in each eye.

gure 10). In most cases, the crossing can be controlled with glasses to correct the hyperopia (Fig. 11); some children require the use of bifocal lenses to fully control the excessive convergence at near gaze. When amblyopia occurs, it is necessary to use occlusion therapy as well as glasses. A few children require surgery for a residual deviation that can not be controlled with glasses alone.

Exotropia

Exotropia is an outward deviation of one or either eye (Fig. 12). It can appear as early as six months of age. The eyes usually go through three phases. In the first phase, the eyes only deviate out intermittently at distance. Visual inattention, fatigue or distance viewing make the eyes go out. For unknown reasons during this phase the child tends to close one eye in the sun. During the second phase, the eyes deviate constantly at distance and intermittently at near and in the third phase, the eyes deviate out at all distances. The treatment of choice is bilateral lateral rectus recession. Better long term stability is achieved if the eyes are aligned during the first phase.

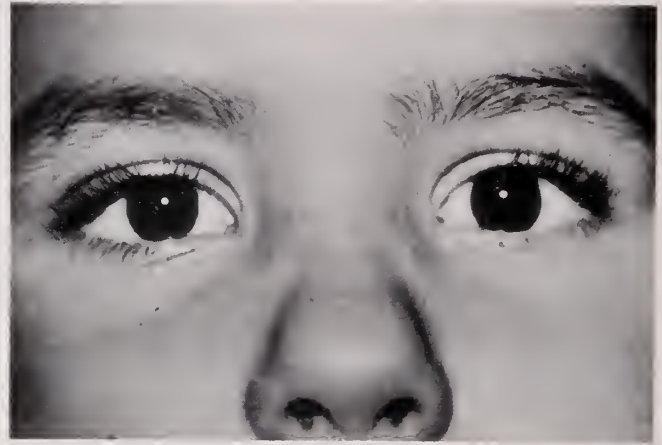


Figure 10: A) Eyes straight looking at distance B) Eyes crossed when looking close.

II Paralytic Strabismus

The discussion of paralytic strabismus is beyond the scope of this presentation. Sufficient is to say that any type of paralytic strabismus can cause a face turn, chin up or down or a head tilt position in order to avoid looking in the direction of the paretic muscle and prevent double vision. Therefore, any patient with an abnormal head position



Figure 11: A) Accommodative esotropia looking at distance, right eye is deviated in. B) Straight eyes when using hyperopic spectacle correction.



Figure 12: Exotropia — Left eye is deviated out.

should have a complete eye exam to exclude this possibility as well as other eye conditions that can cause a similar problem.

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GRAPHICS

ELECTROCARDIOGRAM OF THE MONTH

Oswaldo Jiménez, MD, José R. Couto, MD and Ildefonso Rivera, MD
Cardiology Service VAH, San Juan, P. R.

This 61-year-old white male had been followed in the clinic because of arterial hypertension of 4 years duration. His blood pressure was controlled with methyl-dopa and hydrodiuril. Several days before admission, he started to complain of dyspnea, orthopnea, fatigue and dizzy spells. He had not received digitalis. The electrocardiogram is shown below (Figure 1). The most likely diagnosis is:

- c) Premature ventricular beats and prominent "u" waves;
- d) 2:1 AV block: the site of block located above the His Bundle;
- e) RBBB, PVC's, AV block due to concealed extrasystole.

The results of the intracavitary studies and His Bundle recordings are shown below (Figure 2). The findings indicate:

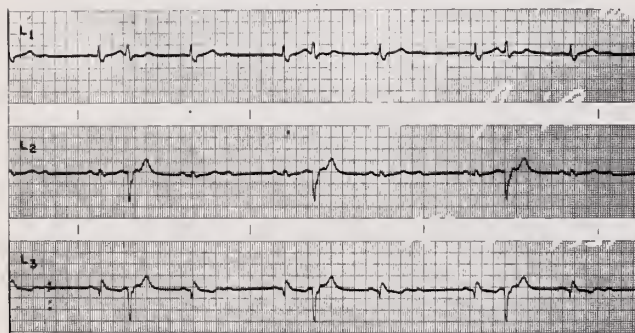


FIGURE 1

- a) RBBB with ventricular trigeminy;
- b) 2:1 AV block: the site of block located below the His Bundle;

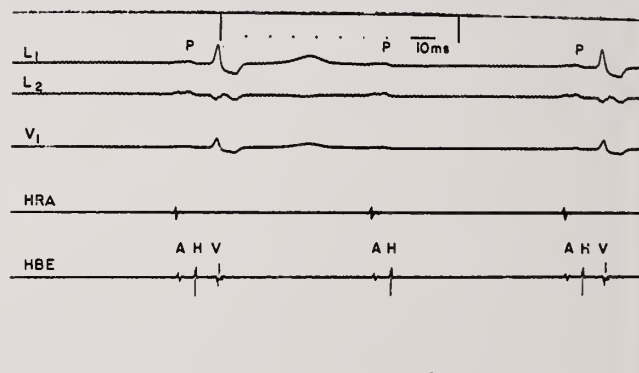


FIGURE 2

- a) The patient should be treated with digitalis and antiarrhythmic agents.
- b) A temporary pacemaker should be inserted as soon as possible.

De la Sección de Cardiología, Hospital de Veteranos, San Juan, Puerto Rico.

- c) The patient should receive oral and intravenous potassium therapy.
- d) None of the above.

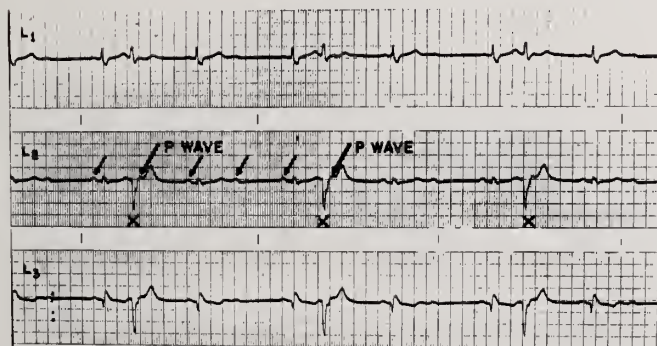


FIGURE 3

ANSWERS:

Question No. 1: (b)

The basic rhythm is sinus. The QRS is wide (.12 seconds) with a terminal deep and broad S wave in lead I. These findings are strongly suggestive of RBBB. Premature contractions are seen throughout the tracing (x). The premature beats are

not preceded by "p" waves, have a wide QRS complex and full compensation pause. These features are typical of premature ventricular contractions (ectopic foci may be located in the posterior division of the left bundle).

The P-P interval (short black arrows) measures 800 msec (rate of "p" waves 75/minute). The premature contractions do not interrupt the sequence of the "p" waves (long black arrows). Two possibilities exist; there is a fixed 2:1 AV block most likely distal to the His bundle or the premature ventricular contractions depolarize in a retrograde manner the His Bundle and A-V node, preventing A-V nodal conduction of the subsequent sinus impulse (short black arrows). However, this phenomenon (concealed conduction) is rare, being most frequently observed with premature beats originating in the His Bundle.

Therefore, the most likely possibility is that of RBBB, 2:1 AV block, the site of block located below the His Bundle since the PR interval is constant before the blocked "p" wave.

Question No. 2:

The intracavitary studies showed a 2:1 AV block, with a His bundle (H) deflection following each atrial depolarization (A).

Question No. 3:

A temporary pacemaker should be inserted.

AVISO DE INTERES

La Junta Editora, consciente de su responsabilidad de hacer que el "Boletín" cumpla a cabalidad con su cometido de divulgar conocimientos médicos, elevar las normas de educación médica y al propio tiempo de llenar las necesidades de todos los compañeros médicos, ha acordado establecer una nueva Sección que se conocerá como "Sección de Preguntas".

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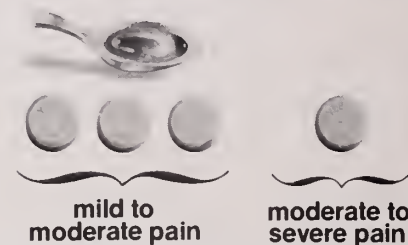
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Esperamos sus preguntas.

Juan M. Aranda, MD
Presidente
Junta Editora

TYLENOL[®] with Codeine

tablets  / elixir 



Summary of Prescribing Information

Description

Tablets: Contain codeine phosphate[®]. No. 1—7.5 mg ($\frac{1}{4}$ gr.); No. 2—15 mg ($\frac{1}{2}$ gr.); No. 3—30 mg ($\frac{1}{2}$ gr.); No. 4—60 mg (1 gr.)—plus acetaminophen 300 mg

Elixir: Each 5 ml contains 12 mg codeine phosphate[®] plus 120 mg acetaminophen (alcohol 7%)

***Warning:** May be habit forming

Actions: Acetaminophen is an analgesic and antipyretic, codeine an analgesic and antitussive

Contraindications: Hypersensitivity to acetaminophen or codeine

Warnings: *Drug dependence.* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration, prescribe and administer with same caution appropriate to other oral narcotics. Subject to the Federal Controlled Substances Act

Usage in ambulatory patients. Caution patients that codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants. Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with this drug may exhibit additive CNS depression. When such a combination is contemplated, reduce the dose of one or both agents.

Usage in pregnancy. Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Pediatric use. Safe dosage of this combination has not been established in children below the age of three

Precautions: *Head injury and increased intracranial pressure.* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries

Acute abdominal conditions. Codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients. Administer with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture

Adverse Reactions: Most frequent: lightheadedness, dizziness, sedation, nausea and vomiting, more prominent in ambulatory than nonambulatory patients, some of these reactions may be alleviated if the patient lies down. Others: euphoria, dysphoria, constipation and pruritus.

Dosage and Administration: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. TYLENOL with Codeine tablets are given orally. The usual adult dose is: Tablets No. 1, No. 2, and No. 3: One or two tablets every four hours as required. Tablets No. 4: One tablet every four hours as required. TYLENOL with Codeine elixir is given orally. The usual doses are: **Children (3 to 6 years):** 1 teaspoonful (5 ml.) 3 or 4 times daily; **(7 to 12 years):** 2 teaspoonful (10 ml.) 3 or 4 times daily; **(under 3 years):** safe dosage has not been established. **Adults:** 1 tablespoonful (15 ml.) every 4 hours as needed

Drug Interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings

For information on symptoms, treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing

TYLENOL with Codeine tablets are manufactured by McNeil Laboratories Co., Dorado, Puerto Rico 00646

Caution: Federal law prohibits dispensing without prescription.

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TYLENOL[®] with Codeine

tablets  / elixir 

Tablets Contain acetaminophen 300 mg plus codeine phosphate* as follows:
No.1—7.5 mg (1/8 gr); No.2—15 mg (1/4 gr); No.3—30 mg (1/2 gr); No.4—60 mg (1 gr)
Elixir Each 5 ml contains 12 mg codeine phosphate* plus 120 mg acetaminophen (Alcohol 7%)

*Warning: May be habit forming.

Please see facing page for summary of prescribing information.

"It hurts when I do this."



In diagnosing work-related musculoskeletal disorders, such as low back pain, it is often helpful to have the patient simulate the motions he does at work.

Dual-acting PARAFON FORTE[®] (chlorzoxazone 250 mg plus acetaminophen 300 mg) tablets

promptly relieves both pain and spasm^{*}

In acute musculoskeletal conditions,^{*}
PARAFON FORTE tablets are:

Dual-acting

combining the effective pain relief^{1, 2} and safety³⁻⁵ of **TYLENOL[®]** acetaminophen and the muscle-spasm reduction of chlorzoxazone

Prompt-acting

clinical studies have shown that patients respond by the first evaluation period (day 2)^{6, 7}

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clinical studies have shown that most patients remain mentally alert when the drug is administered at recommended doses^{7, 8}

Specify no substitution

to make sure your patients get the quality of the PARAFON FORTE brand

DEPOT STOCKED 500's:
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VA 6505-00-764-3313A

Summary of Prescribing Information

***Indications:** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective as an adjunct to rest and physical therapy for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Chlorzoxazone does not directly relax tense skeletal muscles in man

Contraindications: Sensitivity to either component

Warnings: Usage in Pregnancy—Use in women of childbearing potential only when potential benefits outweigh possible risks.

Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped

Adverse Reactions: Occasionally, drowsiness, dizziness, light-headedness, malaise, overstimulation or gastrointestinal disturbances may be noted, rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, chlorzoxazone may possibly have been associated with gastrointestinal bleeding. While PARAFLEX[®] (chlorzoxazone) tablets and other chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately twenty-seven patients, it was not possible to state that the dysfunction was or was not drug induced

Usual Adult Dosage: Two tablets q i d.

Supplied: Light green tablets, imprinted "McNEIL" and "PARAFON FORTE"—bottles of 100 and 500 0972

Caution: Federal law prohibits dispensing without prescription. Full directions for use should be read before administering or prescribing

For information on symptoms/treatment of overdosage, see full prescribing information.

PARAFON FORTE tablets are manufactured by McNeil Laboratories Co., Dorado, PR 00646

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Tail of whipworm
(*Trichuris trichiura*)

Vermox:[®] the only anthelmintic highly effective against whipworm.

	Cure Rate	Egg Reduction
VERMOX [®]	68% [†]	93%
Mintezol ¹	35% [†]	45% ^{††}
Antiminth ²	Not Indicated	
Povan ³	Not Indicated	

Also highly effective against roundworm and hookworm

Since whipworm, roundworm and hookworm are all soil-borne helminths, mixed infections are not uncommon. Only one anthelmintic exhibits high efficacy rates for all three nematodes: whipworm—68%; roundworm—98%; hookworm—96%. That agent is VERMOX.[®]

Please see following page for Summary of Prescribing Information.

**Broad-spectrum coverage
in mixed helminthic infections**

Vermox[®] TABLETS
(mebendazole)



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JPI-023



**Broad-spectrum
coverage in mixed
helminthic infections**

TABLETS **Vermox**[®] (mebendazole)

Contraindications VERMOX is contraindicated in pregnant women (see: Pregnancy Precautions) and in persons who have shown hypersensitivity to the drug.

Precautions PREGNANCY: VERMOX has shown embryotoxic and teratogenic activity in pregnant rats at single oral doses as low as 10 mg/kg. Since VERMOX may have a risk of producing fetal damage if administered during pregnancy, it is contraindicated in pregnant women.

PEDIATRIC USE: The drug has not been extensively studied in children under two years; therefore, in the treatment of children under two years the relative benefit/risk should be considered.

Adverse Reactions Transient symptoms of abdominal pain and diarrhea have occurred in cases of massive infection and expulsion of worms.

Dosage and Administration The same dosage schedule applies to children and adults. The tablet may be chewed, swallowed or crushed and mixed with food. For the control of pinworm (enterobiasis), a single tablet is administered orally, one time.

For the control of roundworm (ascariasis), whipworm (trichuriasis), and hookworm infection, one tablet of VERMOX is administered, orally, morning and evening, on three consecutive days.

If the patient is not cured three weeks after treatment, a second course of treatment is advised. No special procedures, such as fasting or purging, are required.

* Mean cure rate of VERMOX[®] in treating whipworm; cure rate range of 61-75%. Data on file at Janssen Pharmaceutica Inc.

** Mean egg reduction of VERMOX[®] in treating whipworm; egg reduction range of 70-99%. Data on file at Janssen Pharmaceutica Inc.

† Rollo, I.M.: Drugs used in the chemotherapy of helminthiasis, in Goodman, L.S.; and Gilman, A. (eds.): *The Pharmacological Basis of Therapeutics*, ed. 5. New York, Macmillan, 1975, p. 1034.

†† Miller, M.J.; Krupp, I.M.; Little, M.D.; Santos, C.: Mebendazole an effective anthelmintic for trichuriasis and enterobiasis. *JAMA* 230 (10): 1412-1414, Dec. 9, 1974.

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Office on Smoking and Health
Public Health Service Rockville, MD 28057

ABSTRACTOS DE LITERATURA MEDICA

ESTUDIO DE UNA EPIDEMIA DE HEPATITIS NO. A. NO. B. EVIDENCIA DE OTRO POSIBLE VIRUS DE HEPATITIS HUMANA DISTINTA AL TIPO NO. A. NO. B

POST TRANSFUSION

Study of an Epidemic of Non-A, Non-B Hepatitis. Possibility of another human hepatitis virus distinct form post-transfusion Non-A, Non-B Type)

Sulton-Khurdo, M. Am. J. Med. 68: 818-824, 1980.

Una epidemia de hepatitis viral transmitida a través de una fuente común de agua potable fue estudiada en el valle de Kashamir por un período de seis meses, entre noviembre de 1978 y abril de 1979. De 16,620 habitantes en el área estudiada se documentaron 275 casos (1.6 por ciento) casos de hepatitis anictérica en contactos de pacientes con hepatitis viral. Estudios serológicos para Hepatitis B y Hepatitis A no pudieron demostrar ninguno de estos como posible agentes etiológicos. Tanto el curso clínico, período de incubación, forma de diseminación y resultados de las pruebas químicas es semejante al de Hepatitis A, lo cual contrasta al de la hepatitis No. A., No. B. post-transfusión. Este estudio sugiere la posibilidad de otro virus de hepatitis humana que se trasmite a través de una ruta oral-fecal.

(Sometido por Zelma Z. Fuxench Chiesa, MD, VAH)

SACROILITIS PIOGENICA (PYOGENIC SACROILITIS)

Cardon G., Kabins, S. A., Am. J. Med. 69: 50, 1980.

Once casos, siete definitivos y tres probables, de *Sacroilitis piogénica* son presentados y comparados con sesenta y dos casos encontrados en la literatura de habla inglesa. Clínicamente, los pacientes se pueden presentar con una enfermedad localizada subaguda o sistémica aguda. Seis de los once pacientes usaban drogas en forma parenteral. Los síntomas frecuentemente eran no específicos, pero molestias en el área sacroiliaca fueron invariablemente encontradas durante el examen físico. Captación en el área sacroiliaca de citrado de gaglio 67 y/o pirofosfato de tecnecio sugirió el diagnóstico, el cual fue confirmado mediante aspiración articular bajo fluoroscopia cuando los cultivos de sangre fueron negativos. Entre los microorganismos aislados se encontraban bacilos gram-negativos, *Streptococcus* grupo B y un estafilococo. Tratamiento con antibióticos por un período de cuatro a seis semanas fue uniformemente adecuado. Cirugía debe ser reservada para aquellos casos que desarrollan abscesos o secuestro, ninguno de los cuales fue encontrado en esta serie.

(Sometido por Zelma Z. Fuxench, MD, VAH)

REACCIONES DE HIPERSENSITIVIDAD ASOCIADO CON LA ANTITOXINA DE BOTULISMO

HYPERSENSITIVITY REACTIONS ASSOCIATED WITH BOTULINAL ANTITOXIN

Black, R. E., and Gunn, R. A. - *The American Journal of Medicine*, Vol 69, 567-570, October, 1980.

Durante el período de 1967-1977, el centro para el control de enfermedad (CDC) estudió las reacciones de hipersensitividad a la antitoxina de botulismo de origen equino. De 268 personas que recibieron dicha antitoxina, 24 (9.0 por ciento) tuvieron reacciones de Hipersensitividad aguda no fatal (5.3 por ciento) o tardías (3.7 por ciento) a una dosis terapéutica o de piel. La frecuencia de las reacciones no difirió en la edad o sexo del recipiente o con el tipo de antitoxina administrada (AB o ABE). Serum-Sickness ocurrió significativamente más frecuente en personas que recibieron más de 40 ml de antitoxina sérica. La frecuencia de las reacciones fue mayor que la asociada con otros productos de suero equino y probablemente no pueda ser sustancialmente reducida. El riesgo, sin embargo, podría ser sustancialmente reducido, sino eliminado mediante el uso de la globulina inmune de botulismo obtenido de donante humanos hiperinmunizados.

(Sometido por Zelma Z. Fuxench López, MD, VAH)

ENFERMEDAD DE LOS LEGIONARIOS ES RECONOCIDO, COMO UNA CAUSA DE ENFERMEDAD FATAL

J. Am. Med. Ass. 243: 2311-2313, 1980.

La enfermedad de los legionarios es una in-

fección respiratoria aguda, causada por una nueva bacteria gram negativa que fue recuperado primeramente de casos de pulmonía fatal entre individuos de la Legión Americana en Filadelfia. Esta entidad nosológica no solo ocurre en forma de brotes explosivos, sino en forma esporádica o de una manera continua en lugares donde es endémica.

Estos autores realizaron una revisión de pulmones de 224 autopsias del 'Riverside Methodist Hospital de Ohio, ocurrida entre el 11 de abril de 1977 al 10 de abril de 1978. Estos especímenes fueron examinados para *Legionella pneumophila* por tinción con anticuerpos fluorescentes. De 121 pacientes que murieron con pulmonía, *L. pneumophila* estuvo presente en ocho casos (6.6 por ciento). En dos de estos ocho pacientes no ocurrieron síntomas respiratorios importantes, ni fiebre, aunque la pulmonía contribuyó considerablemente en sus muertes. En todos los casos se documentó la existencia de enfermedad subyacente. La enfermedad los legionarios (L. D.), endémica en el área central de Ohio, fue causa de un 3.6 por ciento de las pulmonías nosocomiales en el lugar del estudio. Utilizando la incidencia local de L. D. sobre el número de muertes de adultos anualmente en los Estados Unidos, estos autores concluyen que ocurren muchas muertes asociadas a L. D. cada año. Este estudio resalta la importancia de los tinciones de Dieterle y Antígenos fluorescentes en forma rutinaria durante el examen patológico de tejido pulmonar, especialmente en individuos comprometidos en áreas endémicas.

(Sometido por José L. Maldonado, MD, VAH)

COMPARISON OF EFFICIENCY OF THREE TYPES OF CRUTCHES USING O₂ CONSUMPTION

Dounis, E., Rose, G. K., Wilson, R. S. E., Stevenson, R. D. *Rheumatology & Rehabilitation*, 19: 252-255, 1980.

Artículo cuyo propósito es comparar los tres tipos de muletas más usadas en términos de consumo de O_2 y de comodidad en cuanto al uso por el paciente.

El estudio consistió de poner a 10 sujetos normales, 5 hombres y cinco mujeres entre 23-25 años a caminar una distancia fija usando 3 tipos de muletas diferentes, las axilares, las de codo o Lofstrand y las Canadienses. Al final de cada distancia medían el consumo de O_2 en litros por min. con una máquina portátil. Al final de cada recorrido se le pidió a los voluntarios que evaluaron la comodidad de cada par de muletas desde muy difícil hasta fácil. Se concluyó que el consumo de O_2 para el grupo completo al igual que para hombres y mujeres por separado fue menor con las muletas canadienses que para las axilares y a su vez las axilares consumieron menos que las de codo. En la evaluación subjetiva también la muleta canadiense salió como la más cómoda en su uso.

El estudio recomienda que para personas jóvenes que no tengan enfermedad asociada y que por alguna razón tenga que usar muletas por corto tiempo es recomendable la muleta canadiense por sobre las axilares o las de codo.

(Sometido por José Antonio Arabía, MD)

FAMILIAL CRAMPS AND MUSCLE PAIN

Lazaro, R., Rollinson, R., Fenichel, G. - *Arch. Neurology*, 38: 22-24, 1981.

Una familia cuyos desórdenes se caracterizan por calambres musculares que causan dolor postural de la mano y pies fueron estudiados. Tres generaciones son afectadas y el rasgo es transmitido por herencia autosómica dominante. El desorden comienza en la niñez y no se presume que sea progresivo. Una anomalía primaria en la neurona es sospechada en los estudios básicos de electrofisiología.

(Sometido por E. Baucage, MD)

HEALTH MAINTENANCE EXERCISE: IS IT SAFE FOR THE MIDDLE AGED PATIENT?

Nancy A. Lass, B. S., *Arch Phys. Med. Rehabil.* 61: 566-568, 1980.

Hoy en día hay un interés mayor entre los individuos de todas las edades hacia el ejercicio físico. Una edad avanzada y una pobre condición nos puede conducir a un accidente cardiovascular. Después de un breve reposo de la fisiología del ejercicio, este trabajo bosqueja algunos factores de riesgos y contraindicaciones para el ejercicio y propone una evaluación básica y un programa de mantenimiento para personas de edad media.

(Sometido por R. E. Ortiz, MD)

CARDIAC REHABILITATION: EVIDENCE FOR IMPROVEMENT IN MYOCARDIAL PERFUSION AND FUNCTION

Victor Froelicher, MD, David Jensen, M. A., J. Edwin Atwood, M. D., M. Dan McKiernan, Ph. K., William Ashburn, M. D., John Ross, Jr., MD - *Arch. Phys. Med. Rehabil.* 61: 517-522, 1980.

16 pacientes con enfermedad coronaria (CHD), fueron estudiados durante el reposo y ejercicio con gammagrama o cintigrama de talio y ventriculografía radionuclear; antes y después de entrenamiento con ejercicio durante 3 a 12 meses. Los 5 pacientes presentados en este trabajo demostraron una mejoría tanto en la función de eyección como tolerancia al ejercicio después de la práctica, al mismo tiempo que lograban una capacidad mayor de trabajo. Esta técnica con isotoporadio nucleido provee la primera prueba del mejoramiento en la perfusión del miocardio y la función en pacientes con CHD después de ejercicio de entrenamiento.

Un estudio controlado usando tecnología

avanzada con pacientes clasificados de acuerdo al tiempo del infarto postmiocárdico y por la severidad de la enfermedad está siendo llevada a cabo para confirmar estos hallazgos.

(Sometido por R. E. Ortiz, MD)

CEREBRAL PALSY DIAGNOSIS IN CHILDREN OVER ONE YEAR: STANDARD CRITERIA

Levine, M. S. - *Arch. Phys. Med. Rehabil.* 61: 385-389, 1980.

Perlesia cerebral es un desorden de movimiento y postura no progresivo que en ocasiones tiene hallazgos no-motores. Sin embargo un número de hallazgos motores se requieren para hacer el diagnóstico. Estas anomalías motoras se pueden agrupar en seis categorías: 1) Patrones de postura y movimiento 2) Patrones motores orales 3) estrabismo 4) tono muscular 5) evolución de reacciones posturales 6) reflejos tendinosos profundos, infantiles y plantares.

En una revisión retrospectiva de 60 casos de niños mayores de un año, cuatro hallazgos o más se habían diagnosticado como Perlesia Cerebral; menos de cuatro, rara vez se habrían diagnosticado como tal. Esto es, que descartando las condiciones con trastornos motores progresivos, un niño con cuatro anomalías o más se clasificaría como Perlesia Cerebral.

(Sometido por Frank W. López, MD)

LOW BACK PAIN OF THORACOLUMBAR ORIGIN

Maigne, R. - *Arch. Phys. Med. Rehabil.* 61: 389-395, 1980

Dolor de espalda baja surgiendo de las arti-

culaciones apofisiales de la región toracolumbar es común y frecuentemente atribuido a cambios patológicos en la espalda baja. El diagnóstico es puramente clínico. Los signos clásicos son: "prueba de punto de cresta iliaca" positiva; dolor de palpación localizados sobre los procesos espinosos en la unión toracolumbar y dolor a palpación sobre la articulación apofisial envuelta. Se confirma el diagnóstico bloqueando el dolor con un anestésico local. De 350 pacientes estudiados, 40 por ciento se encontraron con dolor de origen toracolumbar. El tratamiento incluyó manipulación, infiltración con corticoesteroides, electrocoagulación y/o denervación quirúrgica de la articulación apofiseal.

(Sometido por Frank W. López, MD)

CARDIAC REHABILITATION: EVIDENCE FOR IMPROVEMENT IN MYOCARDIAL PERFUSION AND FUNCTION

Froelicher, V., Jensen, D., Atwood, J. E., McKirnan, M. D., Gerber, K., Slutsky, R., Battles, A., Ashburn, W., Ross, J. - *Arch. Phys. Med. Rehabil.* 61: 517-522, 1980.

En el estudio se incluyeron 16 pacientes con enfermedad coronaria estudiados por métodos radioisotópicos con talio en descanso y al ejercicio y ventriculografía antes y después de un entrenamiento con ejercicios por tres a doce meses de duración. Los cinco pacientes presentados demostraron mejoría en la fracción de eyección y en la imagen con talio a la vez que se consiguió un aumento en la carga máxima tolerada.

(Sometido por Frank W. López, MD)

SELF-ESTEEM OF SEVERELY BURNED PATIENTS

Bowden, M. L., Feller, I., Tholen, D., Davidson, T. N., Janes, M. H. - *Arch. Phys. Med. Rehab.* 61: 449-552, 1980.

Como parte de un estudio retrospectivo de rehabilitación en 1977, 320 personas tratadas en un centro de quemados entre 1956 y 1976, fueron entrevistados utilizando un cuestionario de 519 preguntas incluyendo el estado socio-económico y patrón de vida después de la quemadura, 85 por ciento tenían una alta auto-estima. Aunque el tamaño de la quemadura y la parte del cuerpo afectada no afectaron significativamente la edad a la que ocurrió y el tiempo transcurrido si afectaron. Las mujeres desfiguradas tenían auto-estima inferior a los hombres desfigurados. Las personas con baja auto-estima pasaron el doble de días en cama y perdieron mayor número de días de trabajo. Los hallazgos del estudio indican con cierta certeza que la mayoría de los pacientes quemados hicieron ajustes exitosos después de lesiones grandes desfigurantes y que el éxito en la rehabilitación es a largo plazo y de naturaleza episódica.

(Sometido por Jesús Maldonado, MD)

REHABILITATION OF BLIND PATIENTS WITH LOWER EXTREMITY AMPUTATIONS

Altner, P. C., Rusin, J. J., De Boer, A - Arch. Phys. Med. Rehabil. 61: 82-85, 1980.

Doce pacientes ciegos amputados, incluyendo 7 unilaterales y 5 amputaciones bilaterales con una edad promedio de 64 años fueron estudiados. A todos se le proveyó de prótesis y entrenamiento para caminar como pacientes ambulatorios. 75 por ciento de los pacientes ambularon o caminaron dos años o más después de la amputación. 5 regresaron a su nivel preoperatorio de actividad, tres perdieron 1 grado, 4 perdieron 2 o más grados. Todos los pacientes dijeron que la calidad de vida y su propia autoestima fue restablecida con las prótesis.

(Sometido por Ramón E. Ortiz, MD)

LUMBAR FRACTURE DISLOCATION RELATED TO RANGE OF MOTION EXERCISES

Leonid, C., Germer, P. C., Rosen, J. S. Arch. Phys. Med. Rehabil. 60: 182-183, 1979.

Los ejercicios de arco de movimiento son una modalidad terapéutica ampliamente establecida y aceptada para pacientes con lesión de médula espinal. Por lo general resultan inocuos; sin embargo a veces ocurren accidentes, como por ejemplo, fracturas y dislocaciones de extremidades. Se ha reportado una fractura en rebanada ("slice fracture") de L₄ relacionado con ejercicios de arco de movimiento. Le sucedió a un paciente joven que era cuádrupléjico. Pasó de ser un enfermo de neurona motora superior a uno de neuroma motora inferior con las implicaciones vesicales, intestinales y sexuales que ello acarrea. Este tipo de fractura yatrogénica, aunque extremadamente rara, puede prevenirse si los síntomas se interpretan propiamente.

(Sometido por Miguel A. Berríos, MD, VAH)

INCREASE OF MUSCLE STRENGTH FROM ISOMETRIC QUADRICEPS EXERCISES AT DIFFERENT KNEE ANGLES

Margarita Lindh - Scand. Jour. Rehab. Med. Vol. 11: 33-36, 1979.

Ejercicios isométricos para el cuádriceps se efectuaron desde diferentes ángulos con relación a la rodilla, 15° y 60° respectivamente. La fuerza máxima fue valorada en ambas posiciones, antes y después del entrenamiento en 10 mujeres con buena salud. Ambas piernas fueron ejercitadas, una en cada posición. El propósito fue el desarrollar unas reco-

mendaciones prácticas para escoger la posición más adecuada al entrenamiento. El aumento en la fuerza fue mayormente específico al ángulo en el cual la rodilla fue ejercitada. Se sugiere que el ejercicio isométrico preferiblemente se haga a diferentes ángulos en la rodilla para asegurar un aumento total en la fuerza. Los ejercicios isométricos mejoran la fuerza dinámica a baja velocidad, pero no en alta.

(Sometido por Rafael Aguayo, MD)

SURVIVORSHIP IN SYSTEMIC LUPUS ERYTHEMATOSUS - EFFECT OF ANTIBODY TO EXTRACTABLE NUCLEAR ANTIGEN

Marc C. Hobbberg, Carole A. Dorsch, Edward J. Feinglass, and Mary Betty Stevens - Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland - *Arthritis and Rheumatism*, Vol. 24, No. 1 (January 1981)

The course of 81 patients with systemic lupus erythematosus (SLE) who had sera tested for antibody to extractable nuclear antigen (ENA) was studied to determine the effect of the presence of anti-ENA antibody on survivorship. There were no differences in percent survival between the patients with and without antibody to ENA or those with and without antibody to the ribonucleoprotein (RNP) component of ENA. We conclude that there is no prognostic advantage to the presence of either anti-ENA or anti-RNP antibody in patients with SLE.

(Sometido por Edwin Mejías, MD, VAH)

STUDIES ON THE EPIDEMIOLOGY OF ANTIBIOTIC ASSOCIATED CLOSTRIDIUM DIFFICILE COLITIS

Felsety, R., Kim, K. H., Batts, D. H., et al - *Am. J. Clin. Nutr.* 33, 2527-2532, 1980.

Los autores reportan un número de experimentos que han contribuido a esclarecer el síndrome de colitis pseudomembranosa. Sus estudios en animales experimentales demostraron el desarrollo de colitis después de una inyección de antibiótico clindomicina. Los animales con colitis tenían *Clostridium difficile* y la toxina de *C. difficile* en la excreta. El antibiótico vancomicina sirvió para tratar la colitis y previno el desarrollo de colitis si se daba junto con clindamicina. Los autores demostraron un cambio de la flora bacteriana intestinal con reducción del número de peptostreptococos, corynebacterias, y bacteroides y aumento de *Clostridium difficile* y varias otras especies de *Clostridia* después del uso de clindomicina. Sus estudios demostraron que el cambio de la flora intestinal disminuye factores luminales que inhiben el crecimiento de *Clostridia* y que quizás también neutralizan las toxinas de la bacteria. También demostraron que la administración del agente quimioterapéutico metotrexato produce colitis asociado con el sobrecrecimiento de *C. difficile*. Interesantemente documentaron que *C. difficile* se puede cultivar en los cuartos de los pacientes con esta enfermedad y aún en el personal médico y paramédico que cuidan estos pacientes. Recomiendan medidas de aislamiento para prevenir la transmisión de la bacteria de los pacientes con colitis, especialmente a pacientes con predisposición para contagiarse como lo son pacientes tratados con antibióticos.

(Sometido por Angel Olazábal, MD, VAH)

ACTIVIDADES IN VITRO DE LOS ANTIBIOTICOS B-LACTAMICOS Y LOS AMINO-GLUCOSIDOS: UN ESTUDIO COMPARATIVO DE 20 DROGAS DE ADMINISTRACION PARENTERAL

IN VITRO ACTIVITIES OF B-LACTAM AND AMINOGLYCOSIDES ANTIBIOTICS

A COMPARATIVE STUDY OF 20 PARENTERALLY ADMINISTERED DRUGS

Robert J. Fass, MD, *Arch. Int. Med.* 140:763-768, 1980.

Desde la década de los años 70 las penicilinas, las cefalosporinas y los aminoglucósidos son los antibióticos de uso parenteral más frecuentemente prescritos. Desde entonces el número de antibióticos parenterales ha aumentado significativamente. El doctor Fass de Ohio State University College of Medicine estudia la actividad de 20 agentes B-lactámicos y aminoglucósidos en contra de 552 cepas aisladas de pacientes. En este estudio, presenta que los nuevos agentes B-lactámicos no demostraron una mayor actividad que las penicilinas y las cefalosporinas comúnmente utilizadas, en contra de cocos gram positivos. Los nuevos agentes B-lactámicos, particularmente: Mezlocilina, Mecillinam, Cefamandole, y Cefoxitin, con frecuencia demostraron mayor actividad o poseían un espectro de acción más am-

plio en contra de los bacilos gram negativos, haciéndolos útiles en el tratamiento de infecciones causadas por estos.

Los aminoglucósidos estudiados no demostraron poseer actividad en contra de los estreptococos, y los anaerobios; pero sí demostraron actividad en contra de las enterobacterias (*E. coli*, *Klebsiella*, *Enterobacter*) y de los estafilococos.

La Amikacina, al ser más resistente a la degradación enzimática, lo cual representa su mayor ventaja, inhibe 99.2 por ciento de la *Enterobacterias* y *Pseudomonas aeruginosa*. Sisomicina, un nuevo aminoglucósido, demostró ser el agente más activo en contra de los bacilos gram negativo susceptibles a estos agentes. Mezlocilina entre las penicilinas, y cefoxitina entre las cefalosporinas, demostraron ser los agentes más activos en contra de *Bacteroides fragilis*, pero no demostraron tener una mayor actividad en contra de otros anaerobios, y no se consideran los agentes de elección en contra de infecciones por *Bacteroides fragilis*. Se puede considerar su uso en infecciones mixtas por aerobios anaerobios.

(Sometido por Zelma Z. Fuxench Chiesa, MD, VAH)

CONSENSUS STATEMENT – FEBRILE SEIZURES: A CONSENSUS OF THEIR SIGNIFICANCE, EVALUATION, AND TREATMENT

John M. Freeman, MD
Department of Neurology
The Johns Hopkins Hospital
Baltimore

The National Institutes of Health recently convened experts from this country and abroad to present current knowledge about febrile seizures and their consequences, and about the risks and benefits of therapy. This information was presented to a panel under the chairmanship of Dr. Edwin Kendig, former president of the American Academy of Pediatrics. The panel consisted of both academicians and practitioners. The accompanying statement represents the consensus of that panel.

The statement bears reading in its entirety, for it should influence the way that a pediatrician thinks about the child who has had a seizure with fever, how he evaluates and treats that child, and what he tells the parents.

The panel found that there were only two significant risks associated with febrile seizures: a 30 percent to 40 percent risk of recurrent febrile seizures and a slightly increased risk of later epilepsy. They found no evidence of mental or neurologic impairment due to the febrile seizure.

The panel concluded that daily phenobarbital in sufficient dosage to produce a blood level of 15 ug/ml could prevent recurrence of febrile seizures, but that there was *no* evidence that either the administration of phenobarbital or the prevention of recurrences prevented later epilepsy.

Phenobarbital was noted to produce side effects or toxic reactions in up to 40 percent of children. These included behavioral changes, sleep disturbances, and possible interference with learning. Valproic acid was also effective in preventing recurrences, but in view of the rare, but reported fatal hepatitis, liver function tests should be closely monitored.

The consensus panel evaluated the work-up

and the usefulness of laboratory tests and concluded that a complete history, physical examination, and neurologic examination should be performed; a lumbar puncture should be performed if a CNS infection is suspected; and blood chemistries, x-rays and computed tomography scanning, while occasionally useful for diagnosis, were rarely useful in predicting prognosis. Perhaps the most controversial finding was that the EEG, even an abnormal EEG, did not reliably predict the development of epilepsy. Its performance was left to the discretion of the physician, but its prognostic usefulness was questioned.

The panel concluded that in view of the benign nature and outcome of most febrile seizures there was no need for medication. They further concluded that anticonvulsant prophylaxis *may be considered*: (1) in the presence of an abnormal neurologic examination; (2) after a prolonged (greater than 15 minutes) or focal seizure, or one associated with transient or permanent neurologic deficit; or (3) when there is a family history of nonfebrile seizures.

Even when two of these factors are present, only 13 percent of the children develop epilepsy and 87 percent of this "high risk group" will not develop epilepsy. It should be emphasized that there is no evidence that even effective prophylaxis prevents epilepsy.

Perhaps the most effective prophylaxis is a full discussion with parents and caretakers of the benign nature of febrile seizures, of the management of fever, and of first aid for seizures if necessary. With this management few children will need additional medication.

AMA NEWS:

LAETRILE FOUND SAFE IN INITIAL PHASE OF HUMAN STUDY

CHICAGO — Laetrile checks out as safe, says a report in the Feb. 13 Journal of the American Medical Association.

The report is the first phase of the National Cancer Institute's test on humans of amygdalin, or laetrile, under direction of the Mayo Clinic, Rochester, Minn. The first phase involves evaluation of the chemical properties and potential safety of the product. Next phase will be a test on humans of possible anticancer activity.

Laetrile is extracted from bitter almonds and apricot pits, and has been pushed as a remedy for cancer for more than 20 years. Scientific evidence of its usefulness is minimal or nonexistent, but its popularity persists, and the federal government finally decided to sponsor a trial. Many states have passed laws legalizing laetrile within the state, but it still is not licensed by the Food and Drug Administration at a national level, and supplies within the U. S. are limited. Some cancer sufferers have turned to clinics in Mexico for laetrile therapy.

Charles R. Moertel, M. D., head of the study at Mayo, points out that the six patients included in the phase I study was too small a sample to provide results on effectiveness of laetrile. The study sought only to determine whether it is safe to consume.

"The administration of amygdalin according to the dosages and schedules we employed (based on the popular treatment dosages) seems to be free of significant side effects. This conclusion appears validated by early observations in phase II study of 44 Mayo Clinic patients receiving intravenous

amygdalin therapy and 37 receiving oral therapy who have not experienced any symptomatic toxic reaction," Dr. Moertel says.

Several patients had very high blood levels of cyanide, particularly those who ate quantities of raw almonds as snacks. Patients taking laetrile should be warned of possible cyanide poisoning. They should be urged to use only one-tablet doses, to take the tablet well before meals to avoid mixing with food, and to refrain from eating raw nuts, particularly almonds, or fruit pies, he says.

GONORRHEA STRIKES MANY MEN WITHOUT CAUSING SYMPTOMS

CHICAGO — Gonorrhea has leveled off in the United States at around one million cases a year, and has defied the best efforts of the medical community to overcome this common sexually transmitted disease.

A new medical approach to gonorrhea is reported in the Feb. 13 Journal of the American Association. Colorado doctors report on an effort to find and treat men who have gonorrhea but don't know it. The effort, in Colorado Springs and El Paso County, Colo., had proved successful in curbing increases of the disease in the community, despite a large increase in population, says John J. Potterat of the El Paso County Health Department.

Control efforts of health authorities in the past have concentrated on treating men who develop symptoms of gonorrhea, plus seeking out their women partners for treatment. It has long been kno-

wn that many women could be infected but have no symptoms. Only recently has medical science become aware that perhaps as many as 60 percent of infected men also have no symptoms, and can continue to infect their partners unless treated.

Traditional health education messages have made it difficult to convince men that they may have gonorrhea without symptoms, Potterat points out.

"The asymptomatic man has been a shadowy, almost invisible figure in gonorrhea control—an unsuspected and unsuspecting transmitter." Venereal disease program managers who concentrate on trying to reach all sexual partners, both men and women, of infected individuals can anticipate greater success in containing the disease, he says.

Symptoms of gonorrhea in the man are painful, burning urination and discharge of pus from the male organ. Untreated, the infection can last for years. It can result in various physical ills, including sterility. But men also can carry the infection without any of these symptoms.

In women the external genital organs usually are infected first. It can spread to other reproductive organs and is a frequent cause of sterility. There are many other complications of the untreated disease in both sexes.

Doctors now advise both men and women who have been exposed to gonorrhea through sexual contact to visit their doctor or a clinic for tests, even if no symptoms have appeared. The "Silent Clap" is a truly large-scale health problem.

This is an increase of 17,078 over the previous year.

The physician population data is a part of the annual AMA publication, *Physician Distribution and Medical Licensure in the U. S., 1979*, available this month.

There were 356,783 physicians in direct patient care on December 31, 1979. Of those in direct patient care, 70 percent pursued an office-based practice (249,585) with the remaining 30 percent in a hospital-based practice, the AMA book reported.

By specialty, physicians in 1979 were concentrated in internal medicine (68,591), general and family practice (58,130), general surgery (33,217), psychiatry (26,860), pediatrics (26,696), and obstetrics-gynecology (25,215).

Thirty-nine percent of all physicians (178,632) were in a primary care specialty.

As of December 31, 1979, there were 96,605 foreign medical graduate physicians in the U. S. and possessions.

The role of women in medicine has expanded and promises to continue to grow in the future. In 1963 only six percent of all physicians were women: by 1979 the figure was 11 percent. There were 50,604 women physicians as of December 31, 1979.

The volume may be ordered from: Order Department (OP 300), American Medical Association, P. O. Box 821, Monroe, Wis. 53566.

U. S. PHYSICIAN POPULATION CONTINUES STEADY INCREASE

CHICAGO — There were 454,564 physicians in the United States and possessions as of December 31, 1979, the American Medical Association reported.

ANTI-CLOTTING DRUG SLOWS SPREAD OF LUNG CANCER

CHICAGO — A drug that prevents clotting of the blood can slow the growth and spread of cancer, says a report in the Feb. 27 *Journal of the American Medical Association*.

A Veterans Administration Cooperative stu-

dy tested the premise that warfarin sodium, an anti-clotting drug, would modify the course of cancer. The study found that the drug doubled the survival time of individuals with one type of lung cancer, says Leo R. Zacharski, M.D., of the VA Medical Center, White River Junction, Vermont.

The warfarin sodium was added to the treatment program of drugs plus radiotherapy for 25 patients with small cell carcinoma of the lung. These individuals had a median survival time of 50 weeks. A control group of another 25 individuals with the same type of cancer who received drug and radiation therapy without the anti-coagulant recorded a median survival time of 24 weeks, Dr. Zacharski said.

The survival advantage associated with warfarin administration was observed both for patients with extensive disease and for those who failed to achieve complete or partial remission, he said. The warfarin-treated group also demonstrated a significantly increased time to first evidence of disease progression.

"These results suggest that warfarin may be useful in the treatment of small cell carcinoma of the lung and also support the hypothesis that the blood coagulation mechanism may be involved in the growth and spread of cancer in man," Dr. Zacharski said.

Warfarin sodium did not cure the cancers. It served to delay their growth and spread and prolong life. Virtually all of the patients in the study were terminally ill when it began. Only two were still alive within a year after the study was concluded.

INCREASE IN SKIN CANCERS FOUND IN SUN-

BELT RESIDENTS

CHICAGO — More older Americans are retiring and moving to the Southwestern sunbelt to escape the rigors of northern winters. And some of those older Americans are developing malignant melanoma, a particularly virulent type of skin cancer caused by too much sun.

Michael M. Schreiber, M. D., of Tucson, Arizona, reports that incidence of malignant melanoma has been increasing during the past ten years, with a very high rate in southern Arizona. There were 20 malignant melanomas reported in southern Arizona in 1969. The figure climbed to 120 in 1978, and the increase for the ten-year period was 340 percent, Dr. Schreiber says.

The extremely high incidence of melanomas in southern Arizona, the Tucson physician writes, is probably due to meteorologic and geographic factors allowing large amounts of ultraviolet light to reach the earth's surface.

Highest incidence of melanomas was in the age brackets of 50 to 59 and 60 to 69, Dr. Schreiber reports. Most common site was the back, with tumors on the legs second in number.

Writing in the January Archives of Dermatology, a journal of the American Medical Association, the Arizona doctor reports that malignant melanoma is primarily a skin problem for fair-skinned whites.

Dark-skinned whites, Latins, Indians and blacks have relatively little problems from skin cancer.

Tucson has more sunlight, more clear days, and less daytime cloudiness than any other city in North America, he says. Humidity is quite low and temperatures are quite high. Residents wear less and skimpier clothing and spend more time outdoors.



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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

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nents alone is rare. (For a complete list of side effects reported with Limbitrol, please consult full disclosure.)

References: 1. Poulson GW. *NY State J Med* 79: 193-195, Feb 1979. 2. Hollister LE. Antipsychotic medications and the treatment of schizophrenia, chap. 9, in *Psychopharmacology from Theory to Practice*, edited by Borchos JD, et al. New York, Oxford University Press, 1977, pp. 134, 145. 3. Domino EF. Antipsychotics phenothiazines, thioxanthenes, butyrophenones, and rauwolfia alkaloids, chap. 25 in *Drill's Pharmacology in Medicine*, ed. 4, edited by DiPalmo JR. New York, McGraw-Hill Book Company, 1971, p. 476. 4. Sovner R, DiMascio A. Extrapyramidal syndromes and other neurological side effects of psychotropic drugs, in *Psychopharmacology: A Generation of Progress*, edited by Lipton MA, DiMascio A, Killam KF. New York, Raven Press, 1978, p. 1021. 5. Dantson PT, Stenson RL. *Dis Nerv Syst* 37: 629-635 Nov 1976.



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(as the hydrochloride salt)



Efficacy without a phenothiazine

Please see summary of product information on following page.

LIMBITROL® TABLETS Tranquilizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety.
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms including convulsions) similar to those of barbiturate withdrawal for chlordiazepoxide.

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated.

Sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy.

Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extropyromidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) — bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10, Prescription Paks of 50.

How to initiate and maintain therapy

Select dosage strength appropriate for each patient

- Limbitrol 5-12.5 is recommended to minimize drowsiness and for elderly patients.
- Limbitrol 10-25 may be indicated for patients who tolerate medication without undue side effects.

Specify daily dosage based on symptom severity

- An initial dosage of three tablets is recommended.
- Dosage may be increased to six tablets or decreased to two tablets daily as necessary.
- Once a satisfactory response is obtained, patients should be continued on the smallest dose required to maintain the desired effect.

Utilize dosage options to best accommodate individual patient needs

- T.I.D. or Q.I.D., familiar regimens most suited for patients who tolerate medication without undue drowsiness.
- Two tablets one hour before bedtime and one tablet midday may minimize daytime drowsiness and help relieve a common target symptom — insomnia.
- Entire dosage h.s. to take maximum advantage of the sedative effect.

Your guide to patient management... when you decide medication is needed

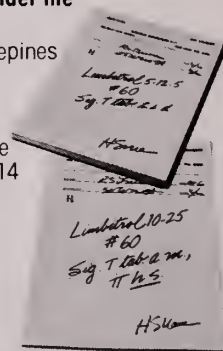
How to make each patient an informed patient

1. Discuss with patients the probability that they will experience drowsiness, especially during the first week.
2. Reassure your patients that drowsiness is one indication that the medication is working and that it may help alleviate their insomnia.
3. Encourage patients to report if drowsiness becomes troublesome so that, if necessary, dosage schedule can be adjusted.
4. Caution patients about the combined effects with alcohol or other CNS depressants. Let them know that the additive effects may produce a harmful level of sedation and CNS depression.
5. Caution patients about activities requiring complete mental alertness, such as operating machinery or driving a car.
6. Warn pregnant patients and patients of childbearing age that the safety of Limbitrol in pregnancy has not yet been established.

Please see complete product disclosure for other pertinent information.

Limbitrol should not be used under the following circumstances:

1. Hypersensitivity to benzodiazepines or tricyclic antidepressants.
2. Concomitantly with an MAO inhibitor. To replace an MAO inhibitor with Limbitrol, discontinue MAO inhibitor for a minimum of 14 days before cautiously initiating Limbitrol therapy.
3. During the acute recovery phase following myocardial infarction.



ROCHE PRODUCTS INC
Manati, Puerto Rico 00701

In moderate depression and anxiety

Limbitrol®

Relief without a phenothiazine

In G.I. therapy



Adjunctive **Librax**[®]

Each capsule contains
5 mg chlordiazepoxide HCl
and 2.5 mg clidinium Br

antianxiety/antisecretory/antispasmodic

for adjunctive therapy of duodenal ulcer* and irritable bowel syndrome*

Librax[®]

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma, prostatic hypertrophy, benign bladder neck obstruction, hypersensitivity to chlordiazepoxide HCl and/or clidinium Bromide.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librax[®] chlordiazepoxide HCl. Roche has no known addi-

tion-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially, increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug.

and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment, blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, i.e., dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

ROCHE

Roche Products, Inc.
Manati, Puerto Rico 00701

"We're together because Dr. Benson recommended home health care."

Home health care is an excellent alternative when your patients cannot fully care for themselves, yet do not need to be in a hospital or nursing home. They can enjoy the comforts of home and family while receiving the care they need, often at a cost far below that of institutional care. And you are always in full control of the plan of care.

Each year, thousands of people receive care at home from Upjohn HealthCare ServicesSM. We employ nurses, nurse assistants, home health aides, homemakers and companions.

We're the nation's leading private provider of home health care, with hundreds of offices throughout the United States and Canada. Many of our offices are licensed to provide services covered by Medicare.

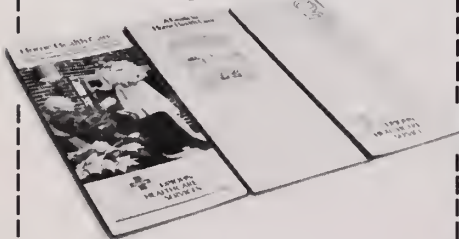
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BOLETIN ASOCIACION MEDICA DE PUERTO RICO

A LA JUNTA EDITORA DEL BOLETIN LE INTERESA SABER SU OPINION Y SUGERENCIAS EN CUANTO AL CONTENIDO DE ESTA PUBLICACION. FAVOR DE CONTESTAR LAS PREGUNTAS EN ESTA HOJA Y DEVOLVERLA EN EL SOBRE ADJUNTO.

CORDIALMENTE,

*Junta Editora
Boletín Médico
Asociación Médica de P. R.*

¿Lee usted el Boletín? ☐ Ocasionalmente ☐ Sí ☐ No

Por favor marque con una (x) el tipo de artículo que le gustaría leer:

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Reportes de Casos	<input type="checkbox"/>
Gráficas	<input type="checkbox"/>
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¿Cuál cree usted que es el mayor defecto del Boletín? _____

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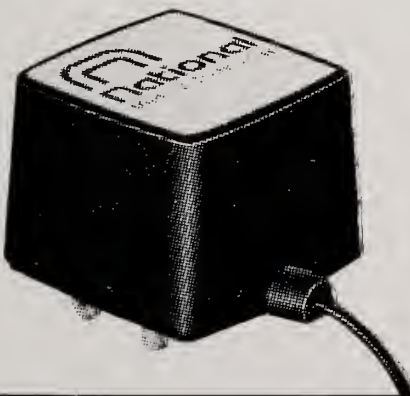
Tipo de práctica de medicina: Privada ☐ Servicio Público ☐
_____ Institucional ☐ Otro: _____

Favor de describir el tipo de medicina que usted mayormente ejerce (medicina general, medicina de familia, cardiología, cirugía, medicina interna, pediatría, oftalmología, etc.) _____

Now you have COOL-LITE for greater patient comfort.

National's COOL-LITE endoscope
takes the heat out of
laryngopharyngeal examination.

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Septra[®] Suspension b.i.d.

Each teaspoonful (5 ml) contains: 40 mg trimethoprim and 200 mg sulfamethoxazole

a consistent performer in
treating acute otitis media
due to susceptible organisms.



Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

IN PEDIATRIC INFECTIONS

A powerful antibacterial performance

The efficacy of Septra has been substantiated in a study of 94 children with acute otitis media due to *H influenzae* and/or *S pneumoniae* (*D pneumoniae*). After 10 days' therapy with trimethoprim/sulfamethoxazole (TMP/SMX), the cure rate was 95.7%.^{1*}

A powerful performance against ampicillin-resistant *H influenzae*†

In another study of 16 children (aged 5–38 months) with purulent otitis media caused by *H influenzae*, it was noted that 10 days' therapy with ampicillin or amoxicillin produced no response in 14 patients. However, after 10 days' therapy with TMP/SMX, 93% of the 14 children responded favorably.² Additional *in vitro* studies have shown that when over 200 isolates of ampicillin-resistant *H influenzae* were tested, all proved susceptible to TMP/SMX.¹

A powerful “double-blockade” method of performing

Septra interferes with or hinders bacterial folate metabolism at two sequential points. This “double-blockade” action is believed to potentiate the effect of the component agents against sensitive bacteria.³

Please note, Septra is not recommended for the treatment of streptococcal pharyngitis. It is contraindicated during pregnancy and lactation, in patients hypersensitive to its components and infants under 2 months of age.

To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.

In vitro data do not necessarily correlate with clinical results.

*The criteria for success were (1) significant clinical response at 72 hours (2) all signs and symptoms normal at day 24.

†To date, clinical data on the effectiveness of Septra in the treatment of acute otitis media due to *H influenzae* with *in vitro* resistance to ampicillin and *in vitro* sensitivity to Septra are limited.

And a powerful plus of good taste

SEPTRA[®] SUSPENSION

EACH TEASPOONFUL (5 ML) CONTAINS: 40 MG TRIMETHOPRIM AND 200 MG SULFAMETHOXAZOLE



WITH A GREAT CHERRY TASTE.

The original pleasant tasting, cherry-flavored Septra® Suspension b.i.d.

Each teaspoonful (5 ml) contains: 40 mg trimethoprim and 200 mg sulfamethoxazole

A consistent performer in treating acute otitis media due to susceptible organisms.

Septra® DS b.i.d.

Each tablet contains: 160 mg trimethoprim and 800 mg sulfamethoxazole

Septra® DS Tablets Double Strength

Septra® Tablets

Septra® Suspension

INDICATIONS AND USAGE:

URINARY TRACT INFECTIONS: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

NOTE: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of these urinary tract infections.

ACUTE OTITIS MEDIA: For the treatment of acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to *Haemophilus influenzae* resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.

SHIGELLOSIS: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

PNEUMOCYSTIS CARINII PNEUMONITIS: For the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

WARNINGS: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A β -hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths associated with administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended; therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

PRECAUTIONS: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Since Septra may prolong prothrombin time in patients on warfarin, coagulation time should be reassessed when Septra is given.

ADVERSE REACTIONS: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. **Blood Dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. **Allergic Reactions:** Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic

myocarditis. **Gastrointestinal Reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. **C.N.S. Reactions:** Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. **Miscellaneous Reactions:** Drug fever, chills and toxic nephrosis with oliguria and anuria. Periarthritis nodosa and L.E. phenomenon have occurred.

Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: The usual adult dosage for the treatment of urinary tract infections is two tablets or four teaspoonfuls (20 ml) every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose — every 12 hours	
lb	kg	Teaspoonfuls	Tablets
22	10	1 (5 ml)	1/2
44	20	2 (10 ml)	1
66	30	3 (15 ml)	1 1/2
88	40	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15–30	Half of the usual dosage regimen
Below 15	Use Not Recommended

PNEUMOCYSTIS CARINII PNEUMONITIS:

The recommended dosage for patients with documented *Pneumocystis carinii* pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. The following table is a guideline for the attainment of this dosage in children.

Weight		Dose — every 6 hours	
lb	kg	Teaspoonfuls	Tablets
18	8	1 (5 ml)	1/2
35	16	2 (10 ml)	1
53	24	3 (15 ml)	1 1/2
70	32	4 (20 ml)	2 (or 1 DS tablet)

HOW SUPPLIED: TABLETS, containing 80 mg trimethoprim and 400 mg sulfamethoxazole — bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100.

ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored — bottle of 473 ml. Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole — Compliance™ Pak of 20, bottle of 60 and unit dose pack of 100.

References:

1. Data on file, Burroughs Wellcome Co.
2. Schwartz R, Rodriguez W, Ross S, et al: TMP-SMX in the treatment of otitis media secondary to ampicillin-resistant strains of *H influenzae*. Second International Symposium on Recent Advances in Otitis Media with Effusion, Columbus, Ohio, 1979.
3. Kucers A, Bennett N Mck: *The Use of Antibiotics: A Comprehensive Review with Clinical Emphasis*, ed 3. Philadelphia, Lippincott, 1978, p 700.



Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

For recurrent attacks of urinary tract infection in women

Bactrim™ DS Double Strength Tablets

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Just one tablet b.i.d. for 10 to 14 days



- Action at urinary/vaginal/lower bowel sites helps eliminate reservoirs of infecting organisms
- Distinctive antibacterial action plus wide spectrum helps eradicate recurrent UTI
- Low incidence of bacterial resistance in community practice

- Convenient *b.i.d.* dosage provides day-and-night antibacterial control
- Contraindicated during pregnancy and the nursing period. During therapy, maintain adequate fluid intake; perform CBC's and urinalyses with microscopic examination.

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.** Note: The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register*, 37:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. **Blood dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. **Allergic reactions:** Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. **Gastrointestinal reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. **CNS reactions:** Headache,

peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. **Miscellaneous reactions:** Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

Urinary Tract Infections: Usual adult dosage—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Recommended dosage for children—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

***Pneumocystis carinii* pneumonitis:** Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: Double Strength (DS) tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, Tel-E-Dose® packages of 100 Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100, Prescription Paks of 40, available singly and in trays of 10. Oral suspension, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

ROCHE

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Bactrim fights uropathogens in the urinary tract/vaginal tract/lower intestinal tract

Please see reverse side for summary of product information.



BOLETIN

ASOCIACION MEDICA DE PUERTORICO

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EDITORIAL: EL PRESENTE Y EL FUTURO DE LA QUIMIOTERAPIA
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INDICE PAGINA 86

Examine Me.

During the past several years, I have heard my name mentioned in movies, on television and radio talk shows, and even at Senate subcommittee sessions. And I have seen it repeatedly in newspapers, magazines, and yes, best-sellers. Lately, whenever I see or hear the phrases "overmedicated society," "overuse," "misuse," and "abuse," my name is one of the reference points. Sometimes even *the* reference point.

These current issues, involving patient compliance or dependency-proneness, should be given careful scrutiny, for they may impede my overall therapeutic usefulness. As you know, a problem almost always involves improper usage. When I am prescribed and taken correctly, I can produce the effective relief for which I am intended.

Amid all this controversy, I ask you to reflect on and re-examine my merits. Think back on the patients in your practice who have been helped through your clinical counseling and prudent prescriptions for me. Consider your patients with heart problems, G.I. problems, and interpersonal problems who, when their anxiety was severe, have been able to benefit from the medication choice you've made. Recall how often you've heard, as a result, "Doctor, I don't know what I would have done without your help."

You and I can feel proud of what we've done together to reduce excessive anxiety and thus help patients to cope more successfully.

If you examine and evaluate me in the light of your own experience, you'll come away with a confirmation of your knowledge that I *am* a safe and effective drug when prescribed judiciously and used wisely.

For a brief summary of product information on Valium (diazepam/Roche)® , please see the following page. Valium is available as 2-mg, 5-mg and 10-mg scored tablets.

Valium®

diazepam/Roche

AVISO DE INTERES

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety, symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal, adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Use in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other anti-depressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. **Adults:** Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed, adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d., adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam/Roche) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500. Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10. Prescription Paks of 50, available in trays of 10.

La Junta Editora, consciente de su responsabilidad de hacer que el "Boletín" cumpla a cabalidad con su cometido de divulgar conocimientos médicos, elevar las normas de educación médica y al propio tiempo de llenar las necesidades de todos los compañeros médicos, ha acordado establecer una nueva Sección que se conocerá como "Sección de Preguntas".

Bajo esta nueva Sección, todos los compañeros tendrán la oportunidad de enviarnos preguntas médicas de casos difíciles o casos clínicos para opinión experta. Estas preguntas, con sus respuestas, serán publicadas en esta nueva Sección.

Las preguntas deberán ser enviadas a:

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Sección de Preguntas
Apartado 9387
Santurce, P. R. 00908

Esperamos sus preguntas.

Juan M. Aranda, MD
Presidente
Junta Editora

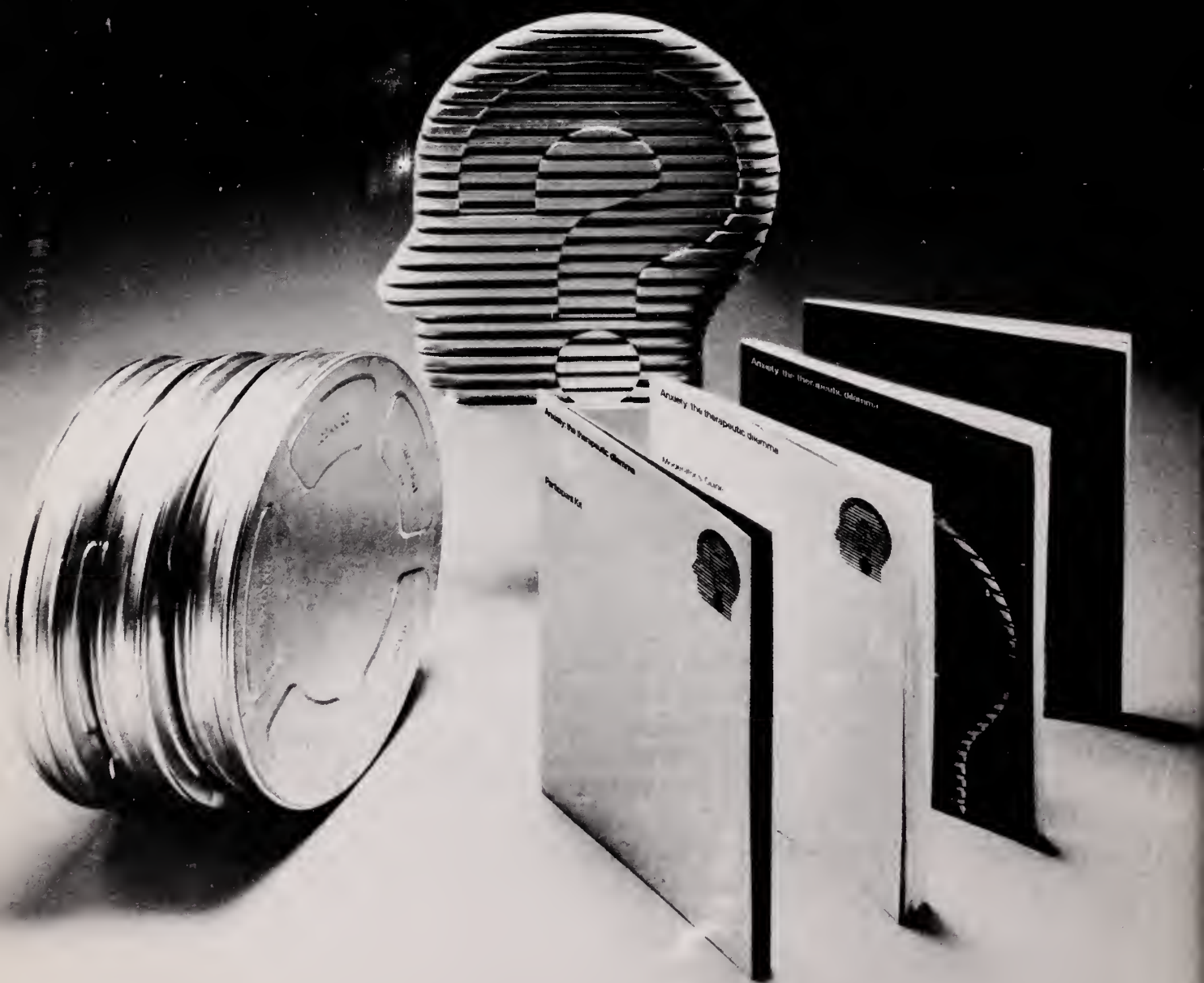


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El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica. El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista. La AMPR no se hace responsable de las opiniones y declaraciones vertidas por los autores y sus puntos de vista no necesariamente representan aquellos de la AMPR, cualquier relación con la política oficial es coincidencia.

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ASOCIACION MEDICA DE PUERTORICO

VOLUMEN 73

INDICE

MARZO 1981

NUMERO 3

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- * Editorial: El Presente y el Futuro de la Quimioterapia Anti-tuberculosa 86
Ramón E. Figueroa Lebrón, MD, FCCP
- * Immunology of Cardiac Diseases - A Review 88
*María L. Santaella, MD, Charles D. Johnson, MD and
Rafael A. Cox, MD*

Santaella, Johnson y Cox presentan en esta edición del Boletín un repaso de los mecanismos inmunológicos de algunas enfermedades cardíacas. Reportan los autores que en el síndrome post-pericardiotomía se han descrito, en varios estudios, anticuerpos cardíacos y que la presencia de éstos se ha correlacionado con la sintomatología clínica.

Anomalías de los linfocitos T se han demostrado en pacientes con infarto agudo del miocardio. Aparentemente la proporción de linfocitos T está baja durante la primera semana del infarto y aumenta progresivamente en las semanas subsiguientes. La carditis reumática y la endocarditis infecciosa son otras dos condiciones que se caracterizan por la presencia de procesos autoinmunes. El evento inicial en la carditis reumática parece ser una respuesta inmune cruzada provocada por el estreptococo grupo A, Beta hemolítico. Como resultado aparecen anticuerpos que reaccionan contra las células del músculo cardíaco. Se ha podido identificar el antígeno en la membrana del estreptococo que reacciona en forma cruzada con el sarcolema cardíaco.

Este artículo será de gran interés para todos y se recomienda como punto de referencia para otros repastos y lecturas.

- * Fascioliasis in Puerto Rico: A Review 94
George V. Hillyer, PhD

Fascioliasis in Puerto Rico is a comprehensive review of the literature with special emphasis on the studies done in Puerto Rico since its documentation in 1904. Specific detail and references are provided concerning infection in man and animal, diagnosis and treatment. This article provides additional information regarding the most frequent parasitic infection found in Puerto Rico.

- * Some Electrocardiographic Faces of Hyperkalemia 102
Charles D. Johnson, MD

Hyperkalemia can present diverse electrocardiographic features. These may vary from peaked T waves to wide QRS complexes with marked changes in the QRS axis in the frontal plane. Several metabolic and electrolytic disturbances may potentiate the

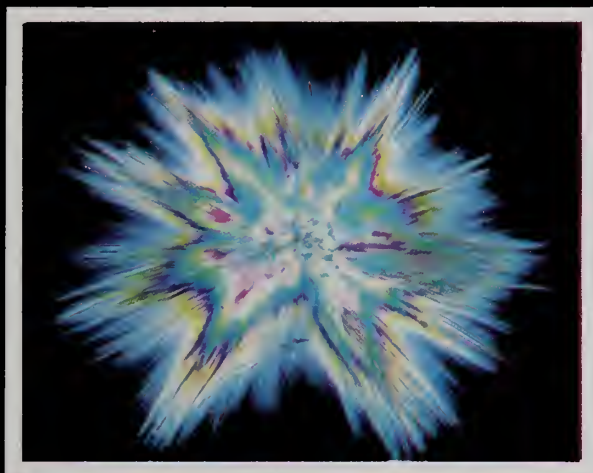
electrocardiographic changes (acidosis, hyponatremia, hypermagnesemia) while saline, bicarbonate, calcium, glucose and intravenous insulin may reverse the electrocardiographic changes. In this issue of the Boletín, Johnson presents in a tabulated form, the most frequent electrocardiographic changes according to the serum potassium level. The patients presented are rather complex in nature, however the EKG tracings are rather useful and helpful in our daily clinical practice. This article, specially the tracings and tables are recommended to all of our readers.

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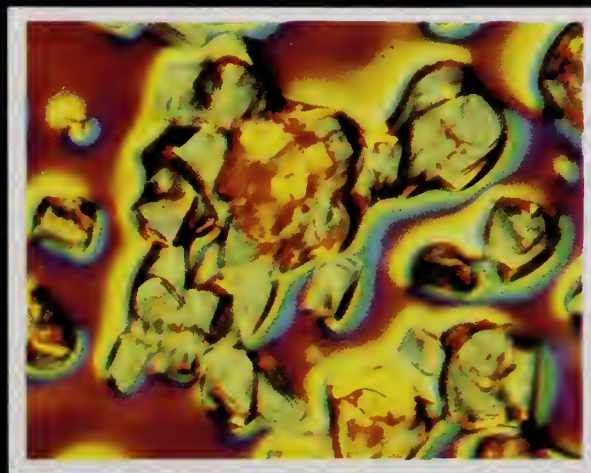


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BRIEF SUMMARY

MINIZIDE® CAPSULES (prazosin hydrochloride/polythiazide) FOR ORAL ADMINISTRATION

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dose so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

INDICATIONS AND USAGE. MINIZIDE is indicated in the treatment of hypertension. (See box warning.)

CONTRAINDICATIONS. RENESE (polythiazide) is contraindicated in patients with anuria, and in patients known to be sensitive to thiazides or to other sulfonamide derivatives.

WARNINGS. MINIPRESS (prazosin hydrochloride): MINIPRESS may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy.

RENESE (polythiazide): RENESE should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Thiazides may be additive or potentiative of the action of other antihypertensive drugs.

Potential occurs with ganglionic or peripheral adrenergic blocking drugs.

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medications such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop with thiazides as with any

potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate the metabolic effects of hypokalemia, especially with reference to myocardial activity.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in hepatic or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be either increased, decreased, or unchanged. Latent diabetes mellitus may become manifest during thiazide administration.

Thiazide drugs may increase responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazides may decrease serum protein-bound iodine levels without signs of thyroid disturbance.

PRECAUTIONS. Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic or mutagenic studies have been conducted with MINIZIDE. However, no carcinogenic potential was demonstrated in 18 month studies in rats with either MINIPRESS or RENESE at dose levels more than 100 times the usual maximum human doses. MINIPRESS was not mutagenic in *in vivo* genetic toxicology studies.

MINIZIDE produced no impairment of fertility in male or female rats at 50 and 25 mg/kg/day of MINIPRESS and RENESE respectively. In chronic studies (one year or more) of MINIPRESS in rats and dogs, testicular changes consisting of atrophy and necrosis occurred at 25 mg/kg/day (60 times the usual maximum recommended human dose). No testicular changes were seen in rats or dogs at 10 mg/kg/day (24 times the usual maximum recommended human dose). In view of the testicular changes observed in animals, 105 patients on long term MINIPRESS therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition 27 males on MINIPRESS alone for up to 51 months did not have changes in sperm morphology suggestive of drug effect.

Usage in Pregnancy: Pregnancy Category C. MINIZIDE was not teratogenic in either rats or rabbits when administered in oral doses more than 100 times the usual maximum human dose. Studies in rats indicated that the combination of RENESE (40 times the usual maximum recommended human dose) and MINIPRESS (8 times the usual maximum recommended human dose) caused a greater number of stillbirths, a more prolonged gestation, and a decreased survival of pups to weaning than that caused by MINIPRESS alone. There are no adequate and well controlled studies in pregnant women. Therefore, MINIZIDE should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether MINIPRESS or RENESE are excreted in human milk. Thiazides appear in breast milk. Thus, if use of the drug is deemed essential the patient should stop nursing.

Pediatric Use: Safety and effectiveness in children has not been established.

ADVERSE REACTIONS. MINIPRESS (prazosin hydrochloride): The most common reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS, some of them rarely (in some instances exact causal relationships have not been established):

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular: edema, dyspnea, syncope, tachycardia.
Central Nervous System: nervousness, vertigo, depression, paresthesia.
Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.
EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.
Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopy studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

RENESE (polythiazide): Gastrointestinal: anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.

Central Nervous System: dizziness, vertigo, paresthesia, headache, xanthopsia.
Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.
Dermatologic: purpura, photosensitivity rash, urticaria, necrotizing angitis, (vasculitis) (cutaneous vasculitis).
Cardiovascular: orthostatic hypotension may occur and be aggravated by alcohol, barbiturates or narcotics.
Other: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness.

OVERDOSAGE. MINIPRESS (prazosin hydrochloride):

Accidental ingestion of at least 50 mg of MINIPRESS in a two year old child resulted in profound drowsiness and depressed reflexes. No decrease in blood pressure was noted. Recovery was uneventful.

Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate that MINIPRESS is not dialyzable because it is protein bound.

RENESE (polythiazide): Should overdosage with RENESE occur, electrolyte balance and adequate hydration should be maintained. Gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium and other electrolyte therapy, administered with caution as indicated by laboratory testing at appropriate intervals.

DOSAGE AND ADMINISTRATION. MINIZIDE (prazosin hydrochloride/polythiazide): Dosage as determined by individual titration of MINIPRESS (prazosin hydrochloride) and RENESE (polythiazide). (See box warning.)

Usual MINIZIDE dosage is one capsule two or three times daily, the strength depending upon individual requirement following titration.

The following is a general guide to the administration of the individual components of MINIZIDE.

MINIPRESS (prazosin hydrochloride): Initial Dose: 1 mg two or three times a day. (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

RENESE (polythiazide): The usual dose of RENESE for antihypertensive therapy is 2 to 4 mg daily.

HOW SUPPLIED.

STRENGTH	COMPONENTS	COLOR	CAPSULE CODE	PKG. SIZE
MINIZIDE 1	1 mg prazosin + 0.5 mg polythiazide	Blue-Green	430	100's
MINIZIDE 2	2 mg prazosin + 0.5 mg polythiazide	Blue-Green/Pink	432	100's
MINIZIDE 5	5 mg prazosin + 0.5 mg polythiazide	Blue-Green/Blue	436	100's



LABORATORIES DIVISION
PFIZER INC.



EL PRESENTE Y EL FUTURO DE LA QUIMIOTERAPIA ANTI-TUBERCULOSA

En poco más de una década; como desde mis años de "residente en Enfermedades Pulmonares" hasta hoy, he visto pasar ante mis ojos y he vivido un gran trajín de ideas primero, estudios después, y luego realidades que han modificado y luego renovado nuestras previas ideas de como tratar eficazmente la enfermedad producida por el Bacilo de Koch.

Comenzó la década del 60 con el uso de tres drogas maravillosas; Isoniacida, estreptomicona y ácido paraminosalicílico. Se conquistaron grandes cosas, se salvaron millones de personas, parecía que por fin habíamos conquistado la cima de la montaña. Como siempre sucede, hay soñadores que ven más allá de la cima conquistada y se preparan a repechar la que está más alta o la que ellos solamente vislumbran.

Se vislumbró entonces encontrar otras drogas que hicieran más fáciles para el paciente y menos tedioso y monótono ese largo camino de diez y ocho o veinticuatro meses de tratamiento que en aquel entonces era "dogma". Perdíamos pacientes no porque las drogas fueran insatisfactorias sino porque el paciente se retiraba del tratamiento por monotonía o por molestias inherentes al tratamiento. Por eso se comenzaron los estudios para ver si era posible el obtener los mismos resultados usando dos en lugar de tres drogas y se empezaron a buscar alternativas que evitaran al paciente las molestias de grandes cantidades de pastillas al día o de inyecciones diarias. Por fortuna, esas alternativas no solo se materializaron sino que el resultado con ellas fue igual de satisfactorio. Así surgió el uso bien generalizado de Etambutol como droga fácil de ingerir, efectiva y de muy pocas complicaciones. Se alcanzó otra cima; pero quedaban otras.

Se pensó y se estudió la posibilidad de que si sería igualmente efectivo el tratar la enfermedad de forma intermitente en lugar de diariamente. Grandes poblaciones en especial de Asia y Africa se beneficiaron de esta alternativa que logró materializarse en otra victoria; en otra cima conquistada. Al comenzar la década del 70 se encuentra la mente soñadora estudiando ya en animales y luego en pacientes otra droga que fuera tan bactericida como la isoniácida y que pudiera tener gran penetración tisular, que fuera fácil de administrar y que tuviese muy pocos si algún efecto secundario. Surge la Rifampicina satisfaciendo todos los requisitos que se le habían exigido. Es con esta droga cuando acaba el presente (de la quimioterapia anti-tuberculosa) y comienza nuestro "futuro".

Comenzamos la década del 80 con dos drogas enormemente efectivas contra la bacteria; de fácil administración oral y pequeñas dosis que pueden ser usadas intermitentemente y que tienen un por ciento bajo de efectos secundarios serios. Ahora, con la re-introducción de la Pira cinamida que en la década del 60 era una droga terciaria y que ahora se le han reconocido atributos antes insospechados se han podido desarrollar regímenes de solo seis meses de duración en los cuales durante el primer mes de tratamiento se administran diariamente Isoniacida, Rifampicina

y Piracinamida y a partir del segundo mes y hasta el sexto se usan solamente Isoniacida y Rifampicina dos veces en semana obteniéndose los mismos resultados que cuando usábamos tres drogas por diez y ocho, veinticuatro meses y a veces por más tiempo. Hoy también se da por aceptado el usar solamente Isoniacida y Rifampicina diariamente por treinta días y luego dos veces en semana por cinco u ocho meses obteniendo los mismos resultados que con el regimen anterior.

Después de comunicarnos con unos personalmente y con otros por correspondencia con los grupos más activos entre los que actualmente están trabajando en la investigación de la quimioterapia Anti-tuberculosa se puede esperar que la década del 80 finalizará con un tratamiento que será capaz en menos de doce semanas usando varias drogas según un itinerario previamente conocido y basado en el momento en que la bacteria sea más susceptible al medicamento indicado obtener igual resultado que con tratamientos que duran más tiempo hoy en día. Se generalizarán las pruebas biológicas indirectas para conocer el "tempo biológico" de la población bacteriana que esté afectando a un paciente en particular y entonces se seguirá el itinerario que para ese paciente se sepa de antemano que va a ser más efectivo en el menor tiempo posible.

Ese es nuestro futuro inmediato porque el "futuro más distante" para algunos de estos investigadores que no dejan de ser soñadores como el Profesor Pilhieu de Argentina, el Profesor Brassent de Francia si repetimos las palabras de ellos "el futuro distante será maravilloso pero hoy sería inaudito el siquiera decirlo".

Ramón E. Figueroa Lebrón, MD, FCCP
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IMMUNOLOGY OF CARDIAC DISEASES- A REVIEW

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Summary: A review is presented regarding currently established and proposed causative immunologic mechanisms and immunologic phenomena related to various primary cardiovascular disorders. This excludes from the presentation those cardiac lesions and/or complications which are seen in association with the so-called autoimmune diseases.

Our aim has been that of providing an organic, updated view of the most relevant literature on the role of immunologic reactions in the pathogenesis of primary cardiac conditions.

Resumen: Se presenta un repaso de los mecanismos inmunológicos establecidos hasta el presente en relación a varias enfermedades cardíacas. Excluye las lesiones cardíacas y/o complicaciones que se asocian a las llamadas enfermedades de autoinmunidad.

Nuestro propósito ha sido el proveer un repaso organizado y actualizado de la literatura más relevante sobre la función de las reacciones inmunológicas en la patogénesis de condiciones cardíacas primarias.

The description of immune reactions has provided insight into the mechanisms involved in diseases of all organ systems. As a result, a role for immunological mechanisms has been shown in cer-

tain diseases of the heart.

In this review, we intend to discuss the entities in the realm of Cardiology in which these mechanisms have been implicated in terms of the pathogenesis of the disease in one way or another. The cardiac manifestations of autoimmune diseases are not within the scope of this review.

Postpericardiotomy Syndrome

This condition results from damage to myocardial and pericardial tissues secondary to trauma, myocardial infarction or surgical procedures. The clinical manifestations of pericarditis, pleuritis and arthralgia resemble those of collagen diseases. Its cause is unknown but there are some interesting observations suggesting that autoimmune phenomena may be involved.

In 1960, Kaplan (1) found autoantibodies in this disorder and then suggested that they might be involved in both rheumatic fever and the post-commissurotomy syndrome. Kaplan and Frengley (2) stated that in both the postcardiotomy and post-infarction syndromes participation of an immune mechanism was likely, as suggested by the latent period and the prompt response to steroid treatment.

The presence of circulating antibodies against cardiac antigens can be demonstrated by several techniques (hemagglutination, immunofluorescence, complement fixation) in up to 80-90 percent of patients after cardiac surgery. On immunofluorescence three main patterns of staining of cardiac muscle fibers have been described: diffuse sarcoplasmic, sarcolemmal-sub-sarcolemmal, and intermyofibrillar.

Several studies (3-8) describe the occurrence of antiheart antibodies in symptomatic and asymptomatic patients with the postinfarction and postcardiotomy syndromes. In general, the total numbers studied are small, yet the data suggests that the antibodies are more likely to be found when symptoms are present. These antibodies could be a result of the cardiac damage, but the observation of Robinson and Bridgen (9) of the symptoms appearing and disappearing in parallel with the presence and absence of antibody respectively, suggest that they may have a role in the etiology of the condition.

Two other areas deserve comment. One is the possibility that the injury (comparable to an infarction) might change the antigenicity of the tissue, thus rendering it more immunogenic. The other refers to the idea of Burch and Colcolough (10) that the entity might be related to reactivation of a latent viral infection. None of these hypotheses have been corroborated unequivocally.

Ischemic Heart Disease

A rise in myocardial antibodies has been shown in 50 percent of patients with acute myocardial infarction, using the indirect fluorescent antibody test as well as the antiglobulin consumption test (11). A more substantial rise in the antibody titers was demonstrated in patients with accelerated or unstable angina, and for this reason the test has been proposed as being useful in detecting subclinical myocardial damage. However, it has not been employed widely for this purpose.

In a study by Agrawal, Gupta, and others (12), anticardiac antibodies and the proportion of T cells were examined in various groups of patients with ischemic heart disease. It was demonstrated that as compared to controls, the proportion of T lymphocytes was low during the first week of acute myocardial infarction, and that the proportions of these cells increased significantly during the second and third weeks postinfarction. The occurrence of anticardiac antibodies varied with respect to the post-insult week: 7 percent incidence during the first week, 46 percent during the second, and 59 percent during the third

week. The study did not show differences in terms of immunological parameters as related to the location and extent of infarction. Anticardiac antibodies were present in a higher proportion of patients with acute myocardial infarction with complications during the first week, but this did not hold for cases during the second or third week. Bauer et al (11) reported that 45 percent of patients with complicated acute myocardial infarction had anticardiac antibody, whereas these were present in 36 percent of uncomplicated cases. The failure to produce cardiotoxicity in vivo or in vitro by anticardiac antibodies is another evidence contributing to the reasoning that these antibodies are the result rather than the cause of cardiac injury. The alterations of T lymphocyte populations have not been defined in terms of specific subpopulations, that is, helper, suppressors, cytotoxic, etc.

Another interesting observation that has been made in patients with myocardial infarction has been that of Ebringer et al (13) who demonstrated that 5 to 7 days post myocardial infarction, serum Ig G levels fall and subsequently become elevated. This type of response was not shown in patients with chest pain without infarction.

Regarding cell-mediated immunity, Wartenberg and Brostoff (14) observed an increased production of leukocyte migration inhibition factor in patients with myocardial infarction.

Sharma et al (15) studied 24 patients with ischemic heart disease for cell-mediated immune response directed to human heart antigen, using the leukocyte migration inhibition test. In those cases with acute myocardial infarction (thirty) the values of the test were higher than in the controls and peaked in 3 to 4 weeks. Post myocardial infarction patients with late complications also had higher values, whereas the values were negligible in all the patients (twelve) with stable angina pectoris. It was suggested that these results could indicate increased and repeated release of cardiac antigens with the subsequent sensitization of T cells.

Finally, Farrell et al (16) have looked into the presence of circulating immune complexes in patients with acute myocardial infarction. Using the solid-phase C1q binding assay, it was demonstrated

that 56 to 66 percent (depending on the assay system used) of the patients studied had circulating immune complexes. These appeared as early as 5 days after infarction but the highest positivity occurred from 2 to 3 weeks post-insult. In all cases, the test was negative by 6 weeks post infarction.

The concept has been proposed that immune complexes containing Ig G antibodies and autoantigens can predispose to thrombosis and heart disease via platelet aggregation and increased vascular permeability (17, 18).

Cardiomyopathies

The reports of anticardiac antibodies in patients with primary cardiomyopathies have been equivocal (19-22). Immunoglobulins bound to both sarcolemmal and sub-sarcolemmal sites have been observed in advanced cases; however these patients seldom show circulating antibodies. These findings have led some authors to suggest that the absence of antibody represents their participation in immune complexes with binding to myocardial antigen.

Maisch et al (23) studied 55 patients with congestive (COCM) and 28 patients with hypertrophic cardiomyopathy (HOCM) to investigate if autoimmune reactions played any role in the pathogenesis of these entities. The index used was the detection of autoantibodies in the patients' sera. In this series, no significant autoimmune phenomena could be demonstrated in patients with HOCM. In respect to COCM, 35 percent of the cases demonstrated heart-specific antiinterfibrillary antibodies indicating severe disease. Also 11 percent of the patients with COCM possessed anti-nuclear antibodies.

Associations of the HLA antigens with disease entities have been cited in numerous cases. Thirty unrelated Japanese patients with HOCM were studied by Matsumori in 1979 (24). No significant differences in frequency of HLA antigens were found in this patient group as compared to controls. In a recent study by Matsumori et al (25) of thirty-three unrelated patients with HOCM, HLA-DRw 4 was found in 73 percent of the cases compared to 33 percent in controls. No significant difference was found bet-

ween controls and cases of hypertrophic non-obstructive cardiomyopathy.

It has been observed that idiopathic congestive cardiomyopathy (ICCM) commonly presents after the resolution of a viral illness and that the pathological findings include lymphocytic and other mononuclear cellular infiltrates, as well as immunoglobulin deposition on sarcolemmal membranes. Fowles et al (26) studied 18 cases with this entity in reference to concanavalin A-induced suppressor T cell activity. Age-matched controls, as well as patients with ischemic congestive cardiomyopathy were also studied. Concanavalin A activated cells from patients with ICCM did not suppress autologous cell responses to either allogeneic mixed leukocyte reaction or mitogenic stimuli. The exact significance of this observation in terms of the disease is not clear, since this is an *in vitro* defect which may or may not reflect an *in vivo* defect in suppressor cell activity.

Chronic Heart Block

Patients with chronic heart block have been shown to have an increased prevalence of autoimmune features such as: vitiligo, hypothyroidism and pernicious anemia (27). In 1977, Fairfax (28) reported that a small group of patients with long-standing heart block possessed a serum antibody which reacts with Purkinje tissue but not with cardiac, skeletal or smooth muscle. The relationship, if any, of this finding to idiopathic heart block remains undefined.

It should be noted that in a previous report by Szako et al (cited in 28), it was shown that the conducting tissue could contain antigens not present in myocardium. The low prevalence of specific conductive tissue antibodies in idiopathic heart block may reflect the long time elapsed since the tissue injury. There has been speculation about the role of cell-mediated immunity in this process but studies have not been conducted in this regard.

Rheumatic Carditis

Rheumatic carditis, a known complication

of acute rheumatic fever, is characterized by auto-immune phenomena. The initial event has been related to cross-reacting immune responses provoked by group A beta-hemolytic streptococci leading to the formation of antibodies that react with heart muscle cells. Antibodies to streptococcal cells have affinity for the sarcolemma and sub-sarcolemmal sarcoplasm of heart muscle fibers. In the cell wall, the antigen appears to be present in a molecular complex with M proteins, which is the virulence factor in group A streptococci (2). Purification of the streptococcal membrane antigen that cross-reacts with sarcolemma has been accomplished.

A cross-reaction has been observed between streptococcal group A carbohydrate and a structural glycoprotein of heart valves (29).

In the various immunopathological findings in rheumatic carditis, the myocardium of all the chambers has been described as infiltrated by globulin (mostly Ig G) and C3 in a study on hearts of children dying of acute rheumatic fever (30). The deposits localized in myofibrils, sarcolemma, interstitial connective tissues and vessel walls. Two possibilities have been considered to explain these findings. One is that antibody to streptococcal antigen (cell membrane) cross-reacts with heart antigen, causing direct damage. The other is that the antibody is directed against decapsulated streptococcal L-forms which have invaded the myocardium.

Sapru et al (31) have shown that in patients with chronic rheumatic heart disease the T cell population is greatly reduced and the lymphocytes of these patients do not respond normally to non-specific stimulation by phytohemagglutinin, but that they do respond to streptococcal membrane antigen. Also, these patients were shown to have reduced levels of CH50 and C3, and this was interpreted by the authors as suggesting that complement-mediated injury might be important. Lymphocytes from patients with rheumatic fever have been shown to be cytotoxic to human cardiac cells.

Infective Endocarditis

Most patients with endocarditis are infec-

ted with bacteria considered to be part of the normal flora of the body, i. e., *Streptococcus viridans*, *Enterococci* and *Staphylococcus aureus*. Therefore, antibody specific for these organisms has been found to be present in the circulation of most individuals prior to the onset of endocarditis. In addition to the specific humoral response in endocarditis patients, a non-specific hypergammaglobulinemia occurs. Elevations of titers of antibodies to a number of non-infecting microorganisms and auto-antibodies, including anti-heart antibodies, antiglobulins and cryoglobulins, also have been demonstrated. This is particularly true of an illness with a duration longer than 6 weeks. Gamma globulin has been found fixed in the sarcolemma and myofibrils of the myocardium, in the walls of blood vessels, especially in the intima and subintima.

A very important concept in terms of the development of valvular infection is the appearance of specific agglutinating antibody. Repeated bacteremia is believed to stimulate the development of a sufficient level of agglutinin to produce conglutination of the small number of organisms. This inoculum attains sufficient size to initiate infection on the previously sterile platelet-fibrin clot. In this system, a high concentration of antibody builds over the years with repeated exposures to the organism, thus creating the conditions for infection to develop.

Heart-reactive antibody has been found in 7 of 9 patients with infective endocarditis by Das and co-workers (32). Three to six weeks post institution of therapy, no levels were detectable. The antibody levels tended to parallel the appearance and disappearance of rheumatoid factor and positive blood cultures. Persistence of myocardial autoantibodies has been regarded to signal impairment of T cell suppressor mechanisms.

Immune complexes forming in antibody excess in patients with subacute endocarditis are large complexes, and they are identified in subendothelial or mesangial deposits in patients with nephritis. On the other hand, complexes formed in antigen excess in acute endocarditis, are smaller and frequently localize as subepithelial deposits.

Bayer et al (33) studied a series of 29 pa-

tients with immune complexes for the presence of complement-containing circulating immune complexes as determined by the Raji cell assay. Twenty-eight of twenty-nine patients revealed significant levels, higher than in patients with sepsis without endocarditis. Immune complexes were correlated with: longer duration of illness, extravalvular manifestations and hypocomplementemia. Patients with right-sided endocarditis showed higher levels than patients with left-sided involvement, and the levels fell to zero with successful antimicrobial or surgical therapy.

Pertinent to cellular immunity, Kauffman et al (34) have shown that DNA synthesis by lymphocytes in response to phytohemagglutinin was reduced in 9 of 16 patients with endocarditis. This depressed lymphocytic response did not correlate with the presence of circulating anti-globulins, hypergammaglobulinemia, or elevated α -macroglobulins.

Cardiac Transplantation

Since the first operation in humans performed in 1967, the problem of preserving the heart for tissue typing has not been solved to satisfaction. Histocompatibility antigens, present on all living nucleated cells, are thought to be as important in cardiac transplantation as they are in renal transplantation.

Acute rejection has been found to be T-lymphocyte-mediated and monitoring this total circulating population has been valuable for detecting early rejection (35). If the T lymphocyte count increases to greater than 300-500/ml. within 30-60 days post transplantation, this usually heralds rejection within the next 2-3 days.

In cases of hyperacute rejection antiheart antibodies are thought to be important. The histology of a rejected heart graft in man suggests that some lesions might be present before transplantation, such as ischemic damage occurring between removal of the donor heart and re-establishment of a coronary circulation and immunosuppressive measures causing cardiac damage.

Rossen et al (36) in a study of 15 human hearts that had been rejected, found IgG, IgA and

IgM in the sarcolemma, muscle fibers and coronary arteries. More immunoglobulin was found in hearts of patients who died of rejection soon after transplantation.

The diagnosis of acute rejection is made by the following clinical features: malaise, weakness, fever, dyspnea, anorexia, progressive signs of heart failure; a pericardial friction rub and triple gallop rhythm may occur. Stinson et al (37) have demonstrated that the electrocardiogram is useful noting the following features: decreased voltage, atrial arrhythmias, rightward deviation of the mean electrical axis and ischemic S-T segment changes. A decrease in QRS voltage has been found to precede acute rejection (38). Histopathological examination of tissue obtained by percutaneous transvenous (internal jugular) biopsy of the right ventricular endomyocardium can confirm the rejection process at an early phase.

Chronic rejection involves the coronary arteries. Lower et al (39) showed that of 17 patients dying beyond six months after transplantation, most have intimal hyperplasia in the coronary vessels, resulting in arrhythmias and heart failure. Histologic examination has shown edema of the vessel wall and damaged and displaced endothelial cells. Fibrin and platelet thrombi have been found deposited on the damaged intima; and organization of these could lead to complete occlusion of the vessel.

Chronic rejection is usually diagnosed only after vascular lesions have led to severe myocardial dysfunction. Kahn et al (40) claim that scintiscanning with ¹³¹ Cesium can reveal areas of decreased myocardial blood flow and function weeks before other clinical manifestations of rejection appear. Routine exercise tolerance testing and echocardiograms have been advocated as useful, as well as coronary arteriography.

The presence of antiheart antibodies is not accepted at present as an adequate technique to monitor rejection since these antibodies can manifest before transplantation or after various surgical and ischemic insults to the heart.

The overall experience recorded in heart transplantation unfortunately reflects failure of two-thirds of the human grafts because of rejection or infection.

A distressing association of lymphoma in 33 percent of the patients less than 40 years old transplanted for idiopathic cardiomyopathy, has been documented by Anderson et al (41).

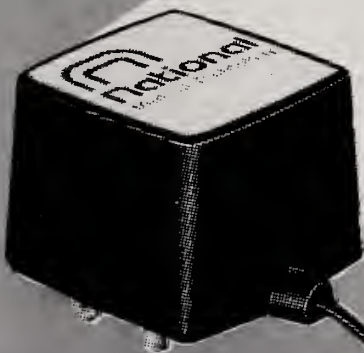
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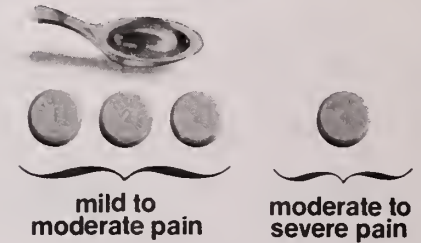
Lung cancer is now an equal opportunity tragedy.

Remember when lung cancer was a man's disease. Because men had been smoking longer than women. But the women's smoking boom that started in the 1930's and 40's—is paying most cruel dividends today. Yet most people still think lung cancer is a man's disease. Tell your female patients the true story. That lung cancer is now an equal opportunity tragedy. That's what "you've come a long way, baby" is all about.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Office on Smoking and Health
Public Health Service Rockville, MD 28057

TYLENOL[®] with Codeine

tablets @ / elixir @



Summary of Prescribing Information

Description

Tablets: Contain codeine phosphate*: No. 1—7.5 mg ($\frac{1}{4}$ gr.); No. 2—15 mg ($\frac{1}{2}$ gr.); No. 3—30 mg ($\frac{1}{2}$ gr.); No. 4—60 mg (1 gr)—plus acetaminophen 300 mg

Elixir: Each 5 ml. contains 12 mg. codeine phosphate* plus 120 mg. acetaminophen (alcohol 7%).

***Warning:** May be habit forming

Actions: Acetaminophen is an analgesic and antipyretic; codeine an analgesic and antitussive.

Contraindications: Hypersensitivity to acetaminophen or codeine.

Warnings: *Drug dependence* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to other oral narcotics. Subject to the Federal Controlled Substances Act.

Usage in ambulatory patients. Caution patients that codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery

Interaction with other CNS depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with this drug may exhibit additive CNS depression. When such a combination is contemplated, reduce the dose of one or both agents

Usage in pregnancy Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Pediatric use. Safe dosage of this combination has not been established in children below the age of three.

Precautions: *Head injury and increased intracranial pressure:* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions. Codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients Administer with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: Most frequent: lightheadedness, dizziness, sedation, nausea and vomiting, more prominent in ambulatory than nonambulatory patients; some of these reactions may be alleviated if the patient lies down. Others: euphoria, dysphoria, constipation and pruritus.

Dosage and Administration: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. **TYLENOL with Codeine tablets** are given orally. The usual adult dose is: Tablets No. 1, No. 2, and No. 3 One or two tablets every four hours as required. Tablets No. 4 One tablet every four hours as required. **TYLENOL with Codeine elixir** is given orally. The usual doses are **Children (3 to 6 years):** 1 teaspoonful (5 ml.) 3 or 4 times daily; **(7 to 12 years):** 2 teaspoonful (10 ml.) 3 or 4 times daily; **(under 3 years):** safe dosage has not been established. **Adults:** 1 tablespoonful (15 ml.) every 4 hours as needed.

Drug Interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings.

For information on symptoms/treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing

TYLENOL with Codeine tablets are manufactured by McNeil Laboratories Co., Dorado, Puerto Rico 00646.

Caution: Federal law prohibits dispensing without prescription.

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McNEIL

McNeil Laboratories, McNEILAB, Inc.
Fort Washington, PA 19034

In the Emergency Department

Potent pain relief without aspirin complications



TYLENOL[®] with Codeine

tablets  / elixir 

Tablets Contain acetaminophen 300 mg plus codeine phosphate* as follows:
No.1—7.5 mg (1/8 gr); No.2—15 mg (1/4 gr); No.3—30 mg (1/2 gr); No.4—60 mg (1 gr)
Elixir Each 5 ml contains 12 mg codeine phosphate* plus 120 mg acetaminophen (Alcohol 7%)

*Warning: May be habit forming

Please see facing page for summary of prescribing information.



Tail of whipworm
(*Trichuris trichiura*)

Vermox[®]: the only anthelmintic highly effective against whipworm.

	Cure Rate	Egg Reduction
VERMOX [®]	68% ^{††}	93% ^{***}
Mintezol ¹	35% [†]	45% ^{††}
Antiminth ²	Not Indicated	
Povan ³	Not Indicated	

Also highly effective against roundworm and hookworm

Since whipworm, roundworm and hookworm are all soil-borne helminths, mixed infections are not uncommon. Only one anthelmintic exhibits high efficacy rates for all three nematodes: whipworm—68%; roundworm—98%; hookworm—96%. That agent is VERMOX[®].

Please see following page for Summary of Prescribing Information.

Broad-spectrum coverage in mixed helminthic infections

Vermox[®] TABLETS
(mebendazole)



JANSSEN PHARMACEUTICA INC.
New Brunswick, N.J. 08903

Committed to research...
because so much remains to be done.
© Janssen Pharmaceutica Inc. 1980 JPI-023



Broad-spectrum coverage in mixed helminthic infections

TABLETS **Vermox**[®] (mebendazole)

Contraindications VERMOX is contraindicated in pregnant women (see: Pregnancy Precautions) and in persons who have shown hypersensitivity to the drug.

Precautions **PREGNANCY:** VERMOX has shown embryotoxic and teratogenic activity in pregnant rats at single oral doses as low as 10 mg/kg. Since VERMOX may have a risk of producing fetal damage if administered during pregnancy, it is contraindicated in pregnant women.

PEDIATRIC USE: The drug has not been extensively studied in children under two years; therefore, in the treatment of children under two years the relative benefit/risk should be considered.

Adverse Reactions Transient symptoms of abdominal pain and diarrhea have occurred in cases of massive infection and expulsion of worms.

Dosage and Administration The same dosage schedule applies to children and adults. The tablet may be chewed, swallowed or crushed and mixed with food. For the control of pinworm (enterobiasis), a single tablet is administered orally, one time.

For the control of roundworm (ascariasis), whipworm (trichuriasis), and hookworm infection, one tablet of VERMOX is administered, orally, morning and evening, on three consecutive days.

If the patient is not cured three weeks after treatment, a second course of treatment is advised. No special procedures, such as fasting or purging, are required.

* Mean cure rate of VERMOX[®] in treating whipworm; cure rate range of 61-75%. Data on file at Janssen Pharmaceutica Inc.

** Mean egg reduction of VERMOX[®] in treating whipworm; egg reduction range of 70-99%. Data on file at Janssen Pharmaceutica Inc.

† Rollo, I.M.: Drugs used in the chemotherapy of helminthiasis, in Goodman, L.S.; and Gilman, A. (eds.): *The Pharmacological Basis of Therapeutics*, ed. 5. New York, Macmillan, 1975, p. 1034.

†† Miller, M.J.; Krupp, I.M.; Little, M.D.; Santos, C.: Mebendazole an effective anthelmintic for trichuriasis and enterobiasis. *JAMA* 230 (10): 1412-1414, Dec. 9, 1974.

1. Registered trademark of Merck Sharp and Dohme.
2. Registered trademark of Roerig.
3. Registered trademark of Parke-Davis.



JANSSEN PHARMACEUTICA INC.
New Brunswick, N.J. 08903

*Committed to research...
because so much remains to be done.*

Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Treatment Can Help Many Alcoholics

Treating Alcoholics

Alcoholism is a very difficult disease to treat, but it can be done.

A certain percentage of alcoholics can be treated successfully, says a pamphlet from the American Medical Association. Not all are hopeless cases.

Most alcoholics should be hospitalized in the early phases of treatment, to treat health problems arising from drinking and to interrupt drinking patterns. Some general hospitals offer treatment programs, other programs are in psychiatric hospitals, and comprehensive centers for alcoholics are available in most larger communities. Personnel especially trained to deal with the physical and social problems function as teams in the treatment centers. Rehabilitation is emphasized.

Treatment is directed toward helping alcoholics find a new way of life free of alcohol. It helps alcoholics to understand and accept their problem, and gives encouragement to overcome the sense of inadequacy that caused the disease initially.

Treatment of alcoholics, no matter how comprehen-

sive, frequently breaks down as soon as they leave the hospital or doctor's office.

On their own again, the alcoholics are face to face with the very real issues of where they will go, what they will do, and what they can expect from others. There is strong likelihood they will be unable to withstand much stress without resorting to alcohol again.

The physician realizes that his role is limited, and that truly remedial treatment requires the combined efforts of many persons in the total rehabilitation of the patient and the family.

Many agencies and organizations concerned with alcoholism belong to the Alcohol and Drug Problem Association of North America. The Association's office (1101 15th St., N.W., Washington, D.C. 20036) will furnish complete information on resources available in any community in the country.

Most states have state-level alcoholism programs and many local government programs exist. Many communities have an Alcoholism Information Center to coordinate local resources.

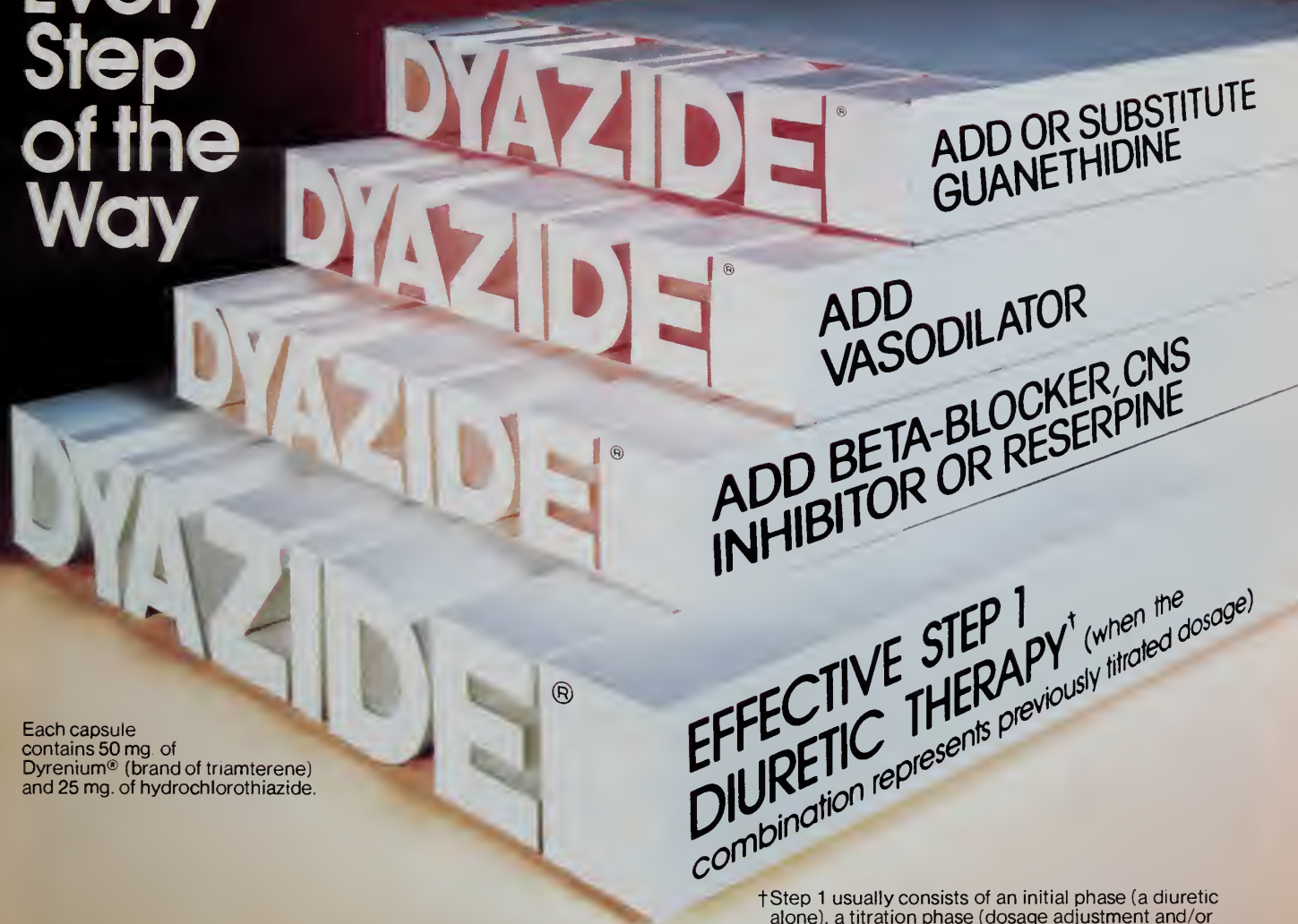
One organization that is successfully aiding alcoholics is Alcoholics Anonymous. There are few communities of any size without a local chapter. AA helps its members achieve and maintain sobriety. It has been extremely valuable to many people.



March, 1981
Frank Chappell
Science News Editor
AMA

In Hypertension*...When You Need to Conserve K⁺

Every Step of the Way



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

EFFECTIVE STEP 1 DIURETIC THERAPY[†] (when the combination represents previously titrated dosage)

[†]Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K⁺ supplement or K⁺-sparing agent) and a maintenance phase (a diuretic alone or in combination with a K⁺ supplement or K⁺-sparing agent).

Serum K⁺ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, throm-

bocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K⁺ frequently, both can cause K⁺ retention and elevated serum K⁺. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Anti-hypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with

possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

©SK&F Co., 1980

SK&F CO.
a SmithKline company
Carolina, P.R. 00630

Colleges shouldn't have to choose between lighting their buildings and enlightening their students.

—Thomas Edison
Inventor

There's nothing more frustrating for a scientist than to be on the verge of a great discovery and not be able to afford the equipment he needs. I know.

When I was a boy, I had to work overtime to get the money I needed for equipment. But somehow I eventually got what I had to have for my experiments.

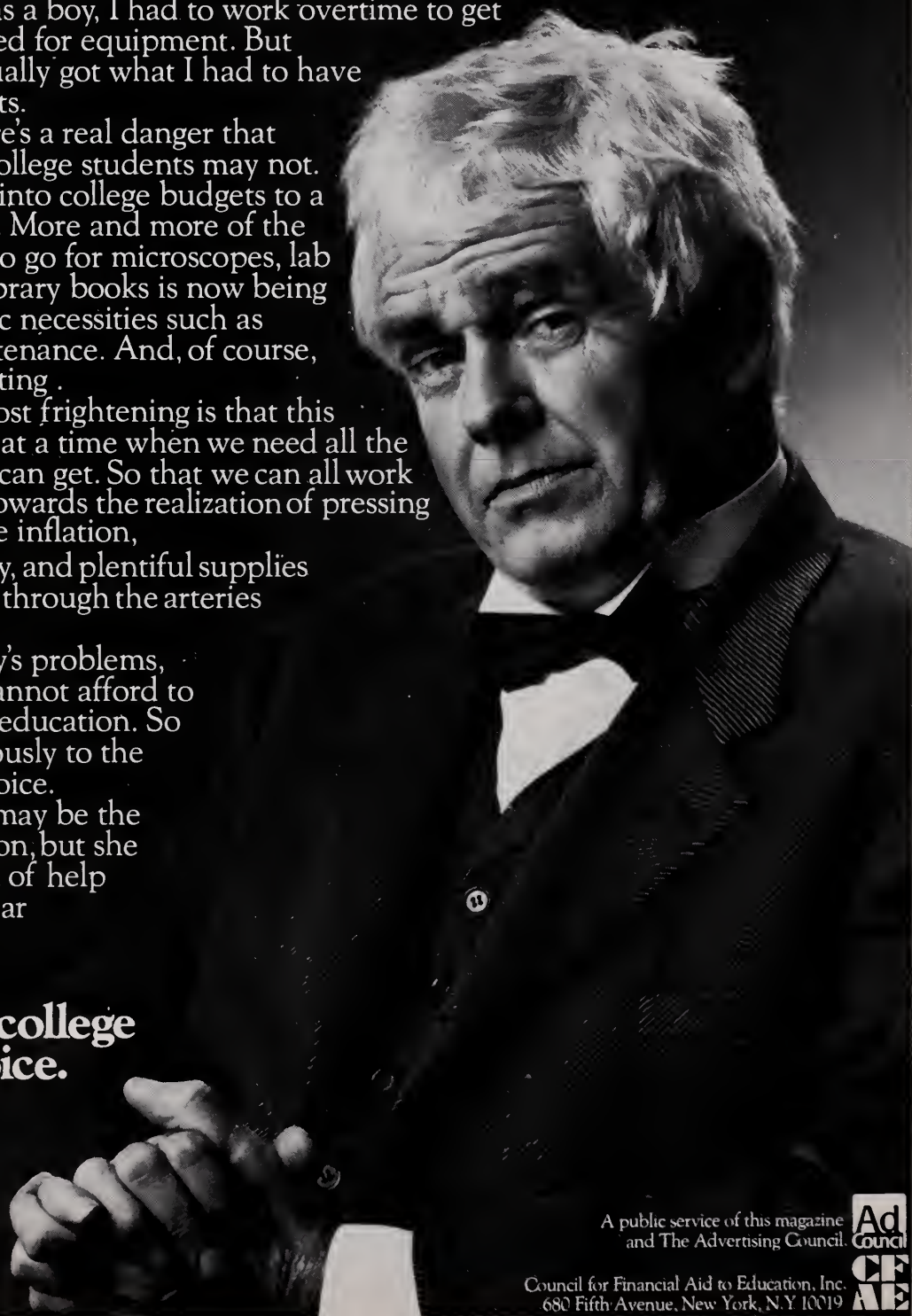
Today there's a real danger that many American college students may not. Inflation is eating into college budgets to a dangerous degree. More and more of the money that used to go for microscopes, lab equipment and library books is now being consumed by basic necessities such as heating and maintenance. And, of course, my specialty—lighting.

What is most frightening is that this squeeze is coming at a time when we need all the trained minds we can get. So that we can all work more effectively towards the realization of pressing goals: manageable inflation, revitalized industry, and plentiful supplies of energy coursing through the arteries of this country.

With today's problems, America simply cannot afford to have second-best education. So please give generously to the college of your choice.

Necessity may be the mother of invention, but she needs a great deal of help if she's going to bear children.

Help!
Give to the college
of your choice.



A public service of this magazine
and The Advertising Council.

Council for Financial Aid to Education, Inc.
680 Fifth Avenue, New York, N.Y. 10019



FASCIOLIASIS IN PUERTO RICO: A REVIEW

George V. Hillyer, PhD

Introduction

Jean de Brie, who had the reputation of being one of the best breeders of cattle and sheep in all of France wrote a treatise in 1379 on wool production and the proper management of sheep. This book, dating from the late Middle Ages, includes the earliest reference to the liver fluke in liver rot in sheep. When Linnaeus gave the definitive Latin name of *Fasciola hepatica* in 1758 to the worm he characterized it as an accidentally swallowed leech whose proper habitat is under stones in fresh water. A fascinating historical review of the elucidation of the life cycle of *F. hepatica* is found in Reinhard (1957).

This report summarizes studies done on fascioliasis in Puerto Rico since its first documentation in man in 1904. The studies suggest that bovine fascioliasis is increasing to hyperendemic proportions and that human fascioliasis is more common than the heretofore suspected, isolated case.

Life Cycle

Infection with *F. hepatica* is acquired when grazing cattle or sheep ingest the stage (metacercaria) of the parasite which is encysted on grass. Humans typically are infected when ingesting the metacercaria which is on watercress. The wall of the metacercaria is digested in the stomach of the mammalian host and the excysted larva burrows through the wall of the gut into the abdominal cavity. Within several weeks the larva has penetrated into the liver tunneling its way through and ingesting the liver parenchyma. By 5-6 weeks post-infection the

worm settles in the bile ducts and 2-3 weeks later is an egg-laying mature worm. At this time (8 weeks post-infection) eggs can be seen in the feces. Although the adult worm is hermaphroditic, cross-fertilization between two worms is thought to be the most common form of sexual reproduction.

The embryos within the eggs undergo cleavage before leaving the interior of the worm. However, the final formation of the ciliated miracidium in freshwater is temperature-dependent. Under optimum conditions in Puerto Rico the formation of a mature, ciliated miracidium occurs within 2-3 weeks after leaving the mammalian host. The egg has an operculum through which the miracidium emerges upon exposure to daylight (Under "experimental" conditions the mature miracidium survives within the egg in water by being stored in the dark). The miracidium swims in freshwater and must find and penetrate a suitable snail intermediate host of the genus *Lymnaea*.

In Puerto Rico the two snail intermediate hosts are *L. cubensis* and *L. columella*. Once inside the snail the miracidium sheds its cilia and is transformed into a sac-like sporocyst, usually in the pulmonary cavity of the snail. As the sporocyst grows new larval forms develop called mother or primary rediae. These rediae break free from the sporocyst and migrate to the digestive gland (also known as "liver" or "hepatopancreas") of the snail. As the mother rediae grow new daughter rediae develop. Eventually these will form cercariae of the gymnocephalus type — with unforked tail, tip without adhesive gland cells, and an excretory canal at the base of the tail. In Puerto Rico the miracidium to cercaria life cycle occurs in 28-30 days when *L. cubensis* is the host and 57-60 days when *L. columella* is the more important snail intermediate host of *F. hepatica* in Puerto Rico (Chiriboga, et al, 1971).

The cercariae emerge from the snail and en-

From the Laboratory of Parasite Immunology, Department of Biology, University of Puerto Rico, Río Piedras, Puerto Rico 00931.

cyst on vegetation. The formation of the metacercaria is a complex process beginning with the loss of the tail and the formation of four cyst wall layers around the head. This process occurs within 24 hours of attachment of vegetation at which time the metacercarial cyst is infective. Under appropriate environmental conditions the cyst can survive for one year. The life cycle continues when the metacercaria is ingested by the mammalian host.

Infection in Man

González-Martínez reported in 1904 the first case of human fascioliasis in Puerto Rico in a male mulatto age 12 in a post-mortem observation finding the worms in the biliary passages. His death was attributed to schistosomiasis, hookworm and pellagra (Ashford and Gutierrez Igaravidez, 1904; González Martínez, 1904). Parenthetically, this was also the first documented case of schistosomiasis mansoni in Puerto Rico (incorrectly designated *Distoma* or *Bilharzia hematobia*). At autopsy, the individual was found to harbor 219 schistosome worms obtained from the trunk of the portal vein and tributaries. In a subsequent survey on the prevalence and clinical features of 136 cases of "intestinal bilharziasis", only one new case of human fascioliasis was found (González Martínez, 1916).

Costa Mandry (1931) reported two additional cases — one from a Venezuelan 45 year old female who had lived in P. R. continuously for 8 years. Her chief complaint was diarrhea with weakness and increasing pallor. In addition to 7 percent eosinophils she was infected with *Ascaris* and *Trichuris*. The second case was a 29 year old Puerto Rican female living in Santurce who had 12 percent eosinophils. Rodríguez Molina and Hoffman (1938) examined in 1929 a "thirty-year old, white, intelligent Puerto Rican farmer...." living in Utuado, a highly endemic area for schistosomiasis. The individual was treated for schistosomiasis with 6 i.v. injections of tartar emetic and in a subsequent examination 3 years later he still had *S. mansoni*, and (in addition) 20 *F. hepatica* eggs "per low power field" were seen in a biliary sediment following duodenal drainage. He had 11 percent eosinophils. This patient had a his-

tory of chewing grass that grew in a swampy area near his home. Clinically, the symptomatology suggested chronic gall bladder disease and gall stones, and the previous physician who treated the abdominal colics before admission believed that surgery was indicated. The discovery of *F. hepatica* eggs averted a surgical operation (see below). The patient was cured of both parasites by treatment with Fuadin and emetine hydrochloride. Another case was of a 39 year old white farmer from Comerío and had a history of eating water cress. He also was infected with both *S. mansoni* and *F. hepatica*. Rodríguez Molina and Hoffman (1938) diagnosed 6 additional cases of human fascioliasis by stool examination during the 1930s. Pons (1937) found eggs of *F. hepatica* in one of 35 patients with intestinal schistosomiasis. Other more commonly found intestinal eggs in association with schistosomiasis were *Necator*, *Ascaris*, *Trichuris*, and *Strongyloides*.

Since the decade of the 1930s, there has been a dearth of information about human fascioliasis. Hernández-Morales (personal communication) saw over one dozen cases in the 1940s. Licha (personal communication) discovered one case at the surgery table. One was discovered at autopsy 3 years ago (Bermúdez, personal communication). López Enriquez and Ramírez Ronda (1978) reported one case of a 40 year old female with a history of eating watercress. She was treated with bithionol but cured with emetine hydrochloride. Prior to cure, her chief complaints were general malaise, nausea, vomiting, and abdominal pain. Her eosinophil levels were low (2 percent). Fiorilli et al (1978) presented an exhaustive clinical review of 6 patients with fascioliasis referred to his group. Three patients were Puerto Rican. The mean duration of illness before diagnosis was 4 months. Fever was invariably present, accompanied by anorexia, vague GI symptoms and disturbances, and marked weight loss. Eosinophilia was present in 4 of the 6 cases.

The above review seems to suggest that human fascioliasis, although present in Puerto Rico, is an extremely rare event. However, the prevalence of bovine fascioliasis appears to be increasing (see INFECTIONS IN ANIMALS) on the Island. In addition, a small survey involving only 184 fecal sam-

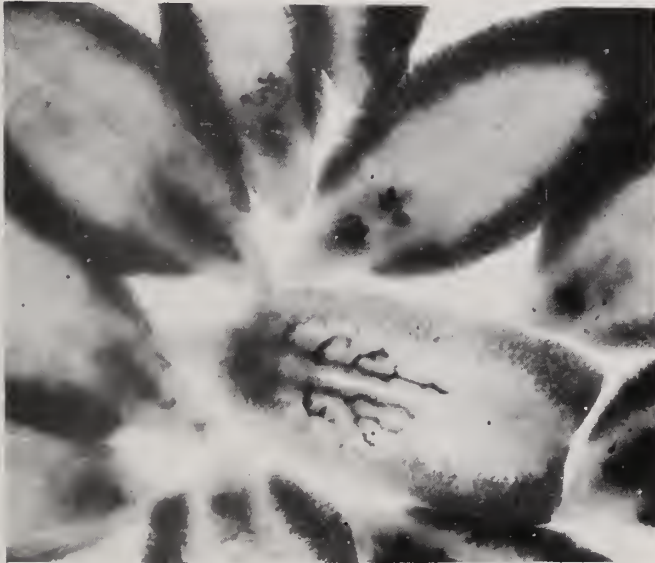


Figure 1: *Fasciola hepatica* adult worms obtained from bovine livers.

ples from people living in the environs of Corozal, Puerto Rico, was conducted. To our surprise 13 individuals were excreting *F. hepatica* eggs and some of these cases were confirmed by serology (Bendezu et al, 1981). All were apparently asymptomatic. Since watercress is cultivated and consumed in the region, this area is hyperendemic for bovine fascioliasis, *Lymnaea cubensis* snails (the intermediate host of *F. hepatica*) have been found in the watercress farms, and animal feces can be washed into the streams, a more frequent occurrence of human fascioliasis should not be unexpected. However, until this study, there was no knowledge on the possible presence of human fascioliasis in this region.

Infections in Animals

González-Martínez (1904) stated that bilharziasis "is a disease of the coastal regions (of Puerto Rico) and in particular of the swampy places, many in which live the infesting larvae next to the cercariae of *distoma* (*Fasciola*) *hepaticum*, this last pa-

rasite diffused enormously among cattle in the North and West of the Island, as we have been able to prove." He did not state whether the South, central or eastern portions of the Island were surveyed.

Bagué (1921) in a mistitled paper on fascioliasis of swine stated that the dry soil and hot sun in the south coast of Puerto Rico resulted in mostly *Fasciola* - free cattle. In addition, the cattle raised near San Juan always had more liver flukes than those from Ponce. He also reported finding *F. hepatica* in a goat. Dickmans (1927, 1929) made the casual observation that a high percentage of cattle slaughtered in Puerto Rico were infected with *F. hepatica*.

Varas Catalá in 1929 investigated on the Island several "epidemics" of bovine fascioliasis, finding the fluke in the livers of all the cattle necropsied. He stated that "these epidemics always occurred when the cattle were maintained in lowland pastures subject to flooding, or fed with grasses obtained from these places." At that time, they observed that a "high percentage" of dairy cows from the Insular Experimental Station had *F. hepatica* eggs in their feces.

Volkenberg (1929, 1931, 1934, 1935, 1936) reported that *F. hepatica* was a common and serious pest of cattle and goats in the wet coastal and lower mountain areas, that it was common in swine that have access to swampy ground, and infrequent, but found, in horses.

Rivera Anaya and Martínez de Jesús (1952) surveyed 38 slaughterhouses in 1948-49 and found that 46,565 head of cattle killed, 7.55 percent (3,515) had "flukey livers." The areas of highest prevalence in this survey were the westcentral zone of Puerto Rico. They estimated that the condemnation of infected livers represented a direct monetary loss of \$20,400.

Chiriboga et al (1971) and De León et al (1972) investigated a total of 19 class A dairy farms from the municipalities of Dorado, Toa Baja and Toa Alta on the Río Plata river basin from January, 1970 to March, 1971. They found in Dorado that 9 of 11 farms had fascioliasis with 11 to 56 percent of the cows positive for the infection. All 5 farms in Toa Baja were positive with infection rates of 5 to

79 percent. The overall infection rate for the 1,229 cows tested by fecal examination was 37 percent. Snails (see Intermediate Host) were found in 14 farms with *L. cubensis* being the most important snail intermediate host as it was found in 13 farms. Infection rates in snails were 27 percent or less, found in 11 farms. Three beef cattle farms located in the Dorado and Loíza areas were also studied. In 1970 the prevalence of infection was very low. In 1971 after heavy rainfall and floods, the 10 cattle examined from Dorado. In Loíza, 46 percent of the *L. cubensis* snails collected were also infected.

In a subsequent study by Chiriboga et al (1980) in the Dorado area in the mid 1970s some 86 percent of the cows in a dairy farm were found positive for *F. hepatica* on coprological examination. The oldest animals in the herd (9-12 years old) had an infection rate of 95 percent whereas the younger animals (3 years old) had infection rates of 71 percent. They also found that the number of snail habitats, the number of snails, and the number of infected snails noticeably increased during the winter months of December through February and that infection occurred chiefly during the months of November through February. Cows in Puerto Rico with a primary infection of *F. hepatica* have a patent period of 40 weeks post-infection after which they are spontaneously cured (De León et al 1981). Thus the high prevalence rate of bovine fascioliasis must be a reflection of lack of immunity and a regular pattern of reinfection.

Frame and Bendezú (1978) and Frame et al (1979) examined the records of all the slaughterhouses in Puerto Rico for the period 1973-1976. The percentage of the cattle slaughtered harboring *F. hepatica* infection steadily increased from 23.9 percent in 1973 to 31.8 percent in 1976. Bovine fascioliasis is probably still rising in Puerto Rico. Frame et al (1980) examined nearly 3,000 fecal samples of dairy cattle from all over the island. Over 64 percent of the cattle sampled were excreting *F. hepatica* eggs with farms near 11 towns having prevalence rates above 80 percent.

The results summarized above suggest that there is a lack of organized effort by the governmental authorities to control transmission of fascioliasis in animals in Puerto Rico.



Figure 2: *Lymnaea cubensis* snails, the principal snail intermediate host of *Fasciola hepatica* in Puerto Rico.

The Intermediate Host

Van Volkenberg (1929) reported that *Lymnaea cubensis* was the intermediate host of *F. hepatica* in Puerto Rico. He based this on experimental studies whereby he infected snails with miracidia obtained from eggs and subsequently infected calves and rabbits with the resulting encysted cercariae. Hoffman (1930) obtained cercariae from field-collected *L. cubensis* snails, allowed them to encyst for 24 hours, and infected guinea pigs with them. Van der Schalie (1948) stated that *L. cubensis* was among the most common freshwater snails in Puerto Rico. Chiriboga et al (1975) observed in areas during the dry season that some "bone-dry" slabs of mud, when moistened in the laboratory with water revealed *L. cubensis* snails two weeks later. They concluded that these snails undergo dehydration and in the field may serve as the nucleus for the snail population in the next rainy season. The maturation period of this snail can be as short as 12 days, with eggs hatching 7 days after being laid. *F. hepatica* cercariae emerge from the snail after 28-30 days of infection (Chiriboga et al, 1971).



Figure 3: Watercress in stream in the vicinity of Corozal, Puerto Rico. Ingestion of metacercariae of *Fasciola hepatica* encysted on this vegetable is probably the principal form of transmission to humans in Puerto Rico.

L. columella is another snail intermediate host of *F. hepatica* in Puerto Rico. The history of this snail in Puerto Rico appears to be obscure as it apparently was not recorded by investigators prior to Van der Schalie in 1948. De León (1970) studied the life history of *L. columella*. Thus snails matured 21-23 days after hatching and the mature snail produced an average of 20 eggs daily, these in turn having incubation periods of 10-13 days. Both eggs and adult snails were highly sensitive to dessication but young snails were resistant. *F. hepatica* miracidia developed into cercariae in 57-60 days in these snails.

Two physid snails, *Physa cubensis* and *Applanoxipha marmorata*, are found in Puerto Rico in aquatica environments, often in association with *L. cubensis* and *L. columella*. These have been shown, however, to be refractive to infection with *F. hepatica* (De León et al, 1971). Strain differences must exist, however, as *Physa cubensis* is an intermediate host for *F. hepatica* in Cuba.

Chiriboga et al (1980) feel that snail control is not useful because the flat and poorly drained pasture land allows water accumulation during the rainy season making molluscicide application expensive and impractical. The observations that snails undergo cryptobiosis during the dry season (see above) compounds the difficulties.

Diagnosis

Definitive diagnosis is done by finding eggs in the feces or in biliary drainage. In the early studies an insensitive simple smear of the fecal sample was done. More recently the method of Dennis et al (1954) which concentrates and quantifies the sample is preferred for diagnosis of bovine fascioliasis. In examining for *F. hepatica* eggs in stool samples from cows the use of iodine to stain the eggs is recommended (Rivera Anaya and Martínez de Jesús, 1951; Dennis, et al, 1954). However, when eggs of both *F. hepatica* and *Cotylophoron cotylophorum* are found in the feces, iodine staining can hinder the differential diagnosis. For this reason De León et al (1975) recommend the use of 0.5 percent methyl green when examining fecal samples from cows as it stains fecal debris, but not fluke eggs. When stained in this manner *F. hepatica* eggs appear in their natural amber color while *C. cotylophoron* (the rumen fluke) eggs appear in their silver color.

In the case of human fascioliasis the most sensitive method is the modified Ritchie formol-ether concentration technique which examines 1 gram of feces (Knight et al, 1976). If a person has been ingesting infected bovine liver, however, a diagnosis of "false fascioliasis" could result. Thus to rely only on stool examinations the patient to be tested must be maintained on a diet free of liver and fecal sam-

ples obtained and examined over a period of several days. An attractive complement to coprology would be immunodiagnosis.

Hoffman and Rivera (1929) performed a tube ring precipitin test testing bovine sera against alcoholic, ether, and other extracts of *F. hepatica*. The test was positive in 48 of 50 infected cows, positive in 39 of 50 uninfected cows, and negative in 11 uninfected cows. Oliver-González et al (1950) used an intradermal test and could differentiate infected from uninfected cows by the size of the wheals formed 30 minutes after injection. Nothing was known regarding the age or intensity of infection of these cows.

In the 1960s Capron and collaborators (1964) in France recommended immunoelectrophoresis for the diagnosis of human fascioliasis. We adapted a new technique, counterelectrophoresis (CEP), for the diagnosis of human and experimental fascioliasis (Hillyer, 1975; Hillyer and Capron, 1976; Hillyer, 1978). One advantage of CEP is that it is rapid—results can be obtained in 30-60 minutes and small (25-30 lambdas) amounts of reactants as needed. In experimental animals such as rabbits, CEP is useful to detect success of chemotherapy thereby having a predictive value of cure (Hillyer and del Llano de Díaz, 1976). Studies on predicting success of chemotherapy by serology in human and bovine fascioliasis are currently in progress. CEP is also superior to indirect hemagglutination in the detection of human and experimental fascioliasis (Hillyer and Allain, 1979).

One problem of serologic tests using crude antigenic extracts is the possibility of cross-reactive antigens between parasites, resulting in false positive reactions. Schistosomes and *Fasciola*, for examples, share common and cross-reactive antigens (Capron et al, 1968; Pelley and Hillyer, 1978; Hillyer, 1979). For example, many individuals infected with *Schistosoma mansoni* react with *F. hepatica* antigens (Hillyer and Capron, 1976). This cross-reactivity can be eliminated by gel filtration of the parasite antigen using Sephadex G-200 (Hillyer and Santiago de Weil, 1977) or Sephacryl S-200 (Hillyer and Santiago de Weil, 1980).

Recently a new highly sensitive and quantitative test has been adapted for the serodiagnosis

of parasitic infections. The use of the test named enzyme-linked immunosorbent assay (ELISA) has been reviewed (Hillyer, and Kagan, 1979). By ELISA, infections in experimental animals can be detected as early as 2-4 weeks of infection (Hillyer and Santiago de Weil, 1979; Levine et al, 1980) and its high sensitivity makes it a logical choice for development in the serodiagnosis of fascioliasis.

Experimental animal models have proven useful as correlates for determining which serologic assays to run when diagnosing human infections. Mice and rabbits infected with *F. hepatica* eliminate parasite eggs in their feces by 8 weeks post-infection (Levine et al, 1980). This is similar to what is observed in humans and cattle. However antibodies can be detected by CEP and ELISA as early as two weeks post-infection with antibody levels being quite high at 4-5 weeks post-infection. Thus a serologic test would be positive at least one month before the infection would be patent and in which parasitologic diagnosis would be possible. Our experience on numerous occasions has been that serodiagnosis has been a valuable adjunct in detecting human infections with *F. hepatica* many cases of which parasite egg excretions levels have been extremely low, or even negative (false negative).

When infected mice, rabbits, or rats are treated at 5-11 weeks post-infection antibody levels drop significantly by four weeks post-treatment when ELISA or precipitation assays such as CEP are used (Hillyer and del Llano de Díaz, 1976; Hillyer and Santiago de Weil, 1979; 1980; Levine et al, 1980). However, in chronically infected rabbits treated at 25 weeks post-infection CEP antibody levels drop rapidly, but ELISA values do not (Levine, et al 1980). This suggests that precipitin tests may be used to predict chemotherapeutic success of a fasciolicidal drug in humans. We in fact were able to demonstrate this with one patient (Wolfe and Hillyer, in preparation).

Acknowledgments

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BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and

related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg (white, scored), 50 mg (aqua) in bottles of 100, 1000 and 5000; 25 mg (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

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Photograph posed by professional model

Please turn page for summary of prescribing information.



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Summary of Prescribing Information

Contraindications: Severe, toxic CNS depression or comatose states from any cause, hypersensitivity to the drug, Parkinson's disease.

Warnings: Usage in Pregnancy: Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards. Infants should not be nursed during drug treatment.

Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity.

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticonvulsant medication since HALDOL haloperidol may lower the convulsive threshold; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants. Concomitant antiparkinson medication, if required, may have to be continued after HALDOL haloperidol is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time. The 1, 5, 10 mg tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Adverse Reactions: CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyra-

midal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn.

Persistent Tardive Dyskinesia: Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by re-institution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms.

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice reported. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecostasia, impotence, increased libido, hyperglycemia and hypoglycemia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration.

The injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

Caution: Federal law prohibits dispensing without prescription.

08628

IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

HALDOL tablets and concentrate (120 ml) are manufactured by McNeil Pharmaceutical Co., Dorado, PR 00646.

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SOME ELECTROCARDIOGRAPHIC FACES OF HYPERKALEMIA

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Summary: This article illustrates some of the manifold faces of hyperkalemia. The electrophysiological and electrocardiographic manifestations of hyperkalemia are tabulated.

Resumen: Este artículo ilustra algunas de las muchas caras de la hiperkalemia. Las manifestaciones electrofisiológicas y electrocardiográficas de la hiperkalemia están tabuladas.

The following patients illustrate some of the manifold faces of hyperkalemia on the electrocardiogram (ECG):

Patient 1 was a 52-year-old male with alcoholic cardiomyopathy, hypertensive cardiovascular disease (HCV), congestive heart failure (CHF), digitalis intoxication and chronic liver disease. ECG traces showed atrial disease, atrial premature contractions (APC) singular and in a run, frequent multiple and multifocal ventricular premature contractions (PVC) (parasystole not definite), incomplete right bundle branch block (RBBB), left ventricular hypertrophy (LVH) and ST-T wave abnormalities. A serum potassium (K) later in the year was normal. Figure 1, when he was taking procainamide and the serum K was 6.9 meq/L, shows large, broad (0.32 S) bizarre QRS complexes (vector is oriented rightward, inferior and anteriorly) at a rate of 115-125

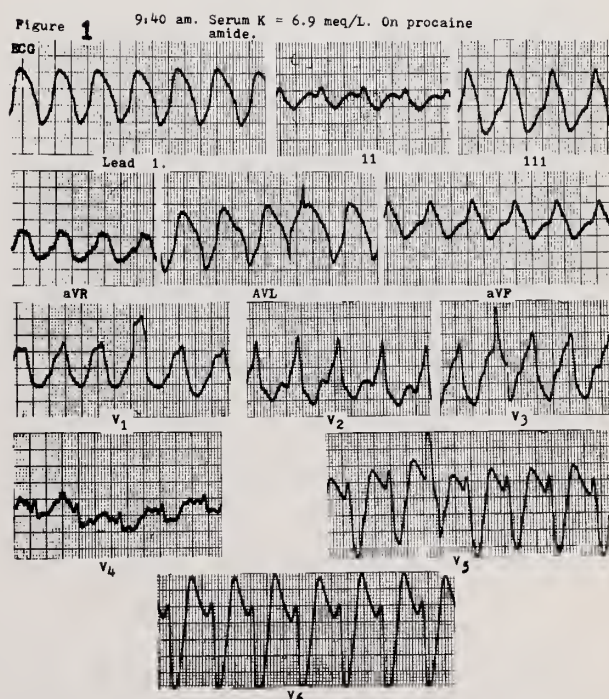


Figure 1: ECG. 8-30-77. P waves are probably absent (Sinoatrial block, arrest or shift of atrial pacemaker). Large, broad bizarre QRS complexes blend with the prominent T waves. The QRS vector is oriented inferior, rightward and anteriorly. R waves are smaller and S waves larger. QS complexes occur in leads 1, aVL and Q waves in V₂. RBBB and LPH (bifascicular block) and pseudoanterior-septal-lateral MI are suggested. See text.

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per minute, blending with prominent T waves. The Q-T interval = 0.50 S. The ST segments appear elevated in leads

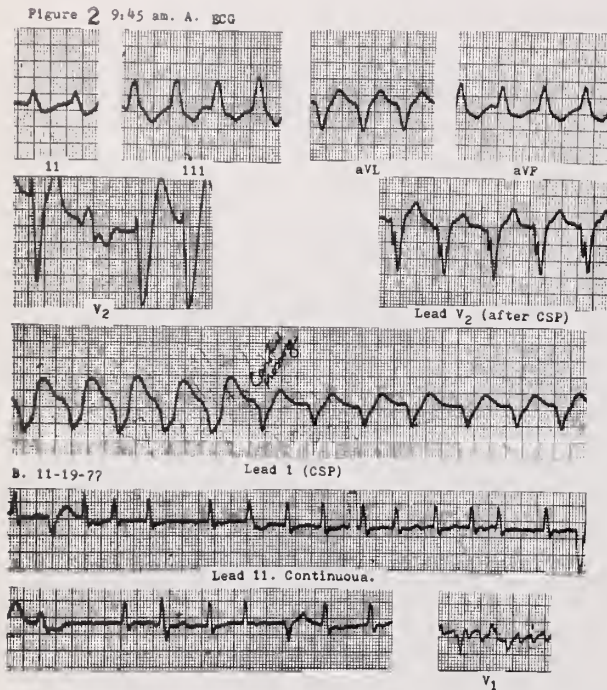


Figure 2: Minutes later. P waves of low amplitude probably exist in V_2 . A. CSP slows and produces less wide QRS complexes. Procainamide toxicity may also be present. B. $K = 6.1$ meq/L. Atrial flutter. PVC's. RBBB.

I, aVL and depressed in leads II, III, aVF, V_{2-4} . No definite atrial activity is delineated. The R waves are smaller and S waves deeper and wider. QS complexes occur in leads I, aVL and a Q in V_2 . RBBB with left posterior hemiblock (LPH) or slow ventricular tachycardia (VT) are suggested. Figure 2 A was obtained minutes later. The QRS complexes remain broad (0.26 S) with a rate of 100-115. P waves of low voltage are probably present in V_2 . Carotid sinus pressure causes slowing and less widened QRS complexes. After therapy with antiarrhythmic drugs and for hyperkalemia the complexes become more normal. Both hyperkalemia and procainamide toxicity (which can produce sinoatrial node depression with junctional and ventricular escapes, prolongation of the P-R, QRS and Q-T intervals, atrioventricular [AV] and intraventricular conduction slowing and ventricular fibrillation-Vf) are probably playing roles in Figures 1 and 2 A. A supraventricular tachycardia (SVT) with sinoventricular conduction could explain the patterns. Fi-

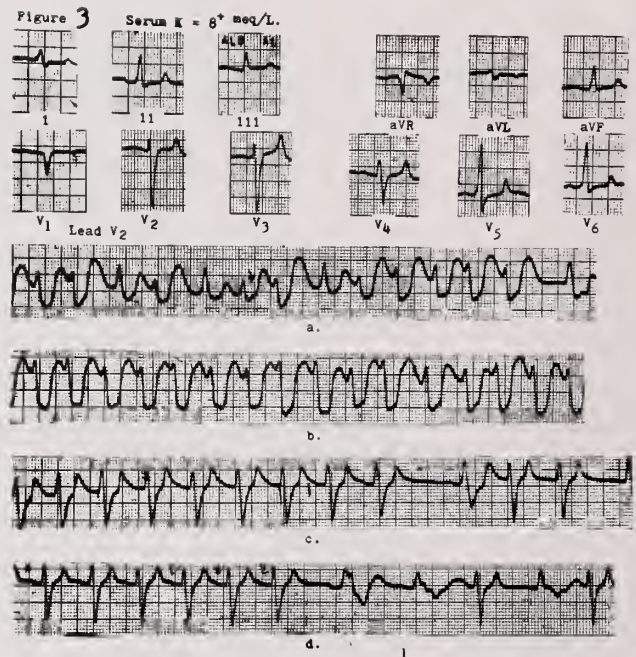


Figure 3: $K = 8^+$ meq/L. Moderate-advanced hyperkalemia. Low amplitude P waves-sinus tachycardia. First degree AV block. Peaked symmetrical T waves. QRS complexes show broad deep S waves.

gure 2 B (no procainamide), $K 6.1$ meq/L, shows RBBB, PVCs and atrial flutter. A small r wave is present in V_2 . The 2d beat after the pause in the lower lead II strip is conducted more aberrantly.

Patient 2, Figure 3, are traces of a 28-year-old male with chronic renal disease (CRD) and a K of 8^+ meq/L. The upper ECG shows low amplitude P waves, first degree AV block in some leads, 0.16 S QRS interval with late slowing, a Q-T of 0.44 S and peaked symmetrical T waves. Strips a-d are V_2 rhythm strips with broad (especially broad deep Ss) QRSs of variable configuration and rate, peaked Ts and small P waves becoming visible in Strips c and d. The QRS complexes ending the pauses differ in appearance - sinus tachycardia. Reversible moderate to advanced hyperkalemia is presented.

Patient 3, Figure 4, was a 67-year-old female with

Figure 4. 5-9-78. Serum K = 7.7 meq/L (5-10-78).

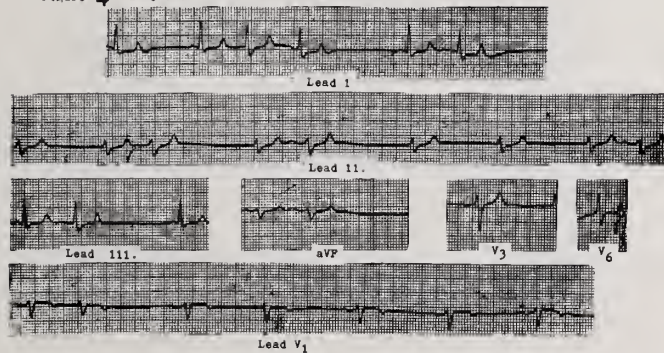


Figure 4: Sinus bradycardia and sinoatrial block. APC's with first degree AV block. Perhaps concealed conduction. Sick sinus Syndrome type pattern. RBBB and LAH.

Figure 5 Serum K = 6.8 meq/L.

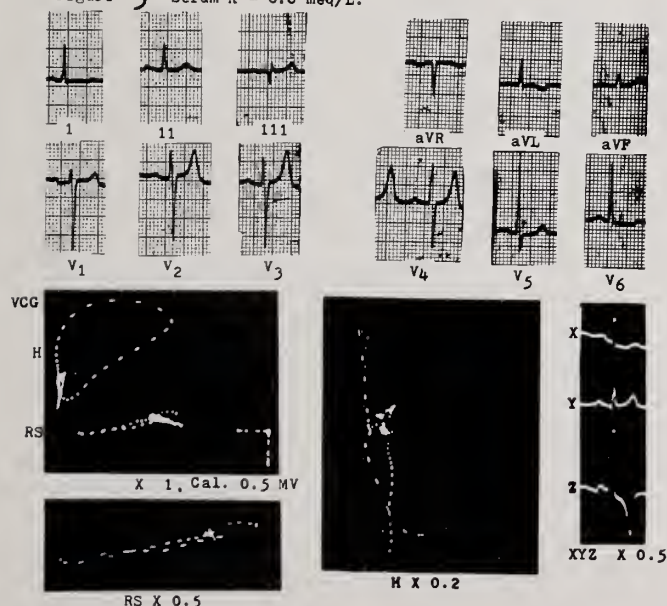


Figure 5. K = 6.8 meq/L. ECG- Peaked T waves in leads V_{1-5} . VCG - T loop oriented + 90 degrees anterior, inverted T in lead Z.

CRD (K = 7.7 meq/L, sodium [Na] 120 meq/L, Bun 192 mg/100 ml), CHF and a digoxin level of 1.5 ng/ml. A grossly irregular rhythm with sinus bradycardia, variable low amplitude or absent P, atrial arrest or second degree sinoatrial block,

junctional escape, two APCs with first degree AV block, atrial bigeminy with aberration (unstable sinus mechanism), a Q-T interval of 0.44 S, left axis deviation, RBBB, peaked T and only tiny U waves are noteworthy. A Sick Sinus syndrome type behavior and concealed conduction may exist. The arrhythmias resided at K levels of 5.6-5.7 meq/L. Normal sinus rhythm, APC's and minor ST-T wave changes (normal K) were observed later.

Patient 4, Figure 5, was a male with diabetes mellitus and hyperkalemia of 6.8 meq/L. There are peaked T waves in V_{1-5} which are diphasic in leads I, V_6 and inverted in aVL and lead Z. The vectorcardiogram (VCG) shows a + 90 degrees anterior T loop.

Figure 6

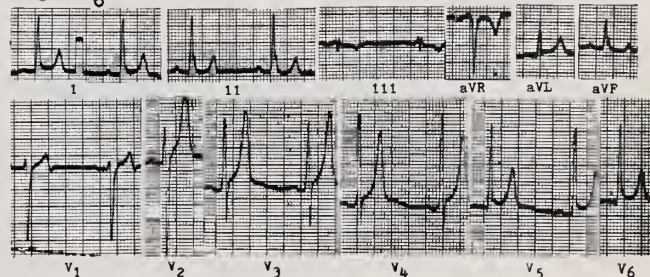


Figure 6. ST segment elevation. Large tented symmetrical T waves.

Patient 5, Figure 6, was a 42-year-old male renal case whose K level is not known. There are anterior and lateral ST elevation and huge tented symmetrical T's; only tiny U waves are seen.

Patient 6 was a 61-year-old male with CRD, hypertension and no myocardial infarction (MI) (autopsied). Serum K were 7.5, 8, Na 120 and $CO_2 < 10$ meq/L. Irregular QRS complexes with accentuated S waves, and absent P and U waves were evident. QS complexes manifested in aVF and one PVC.

Patient 7, Figure 7, was an 80-year-old male with metastatic adenocarcinoma of the prostate, acute renal failure (ARF), CHF and atherosclerotic heart disease who was undergoing dialysis. An ECG (K 5.4 meq/L, Bun 69) showed only a nonspecific T abnormality. Another trace (12-27-71) showed large broad irregular QRS's fusing with ST-T

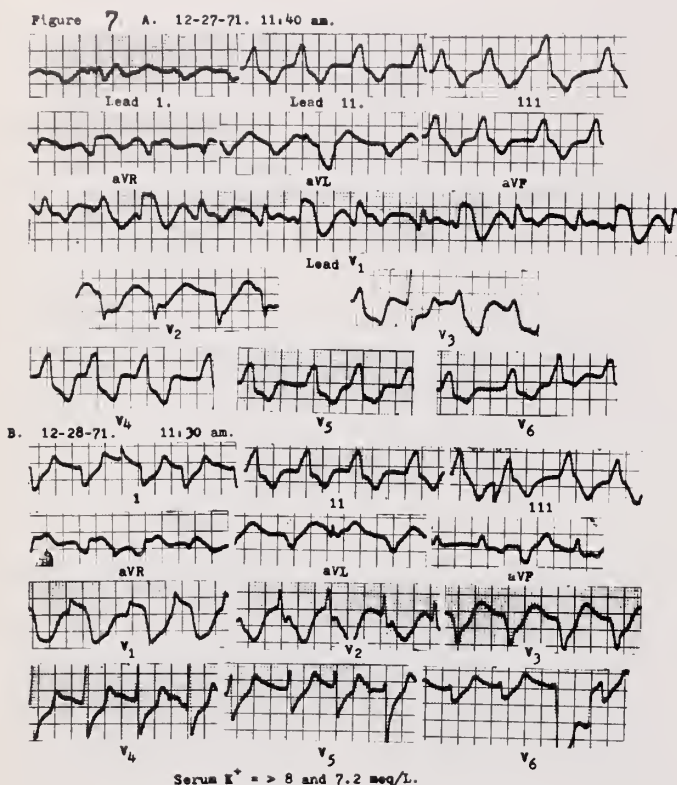


Figure 7. Advanced to Far-Advanced Hyperkalemia. A. Absent P waves. Pattern of both RBBB and LBBB, and LPH. Axis = 100-105 degrees. QR in V_1 and QS in leads I, aVL and V_2 . B. Ugly RBBB and LPH. Axis = 100-105 degrees. QS in leads I, aVL, V_3 . ? PVC's.

waves (rate 100), RBBB and LPH (axis + 135 degrees) and prolonged Q-T interval when the K was 8, 8.3 and the CO_2 < 10 meq/L. Later on the same day, Figure 7 A, different QRS patterns appear manifesting features of both RBBB and left bundle branch block (LBBB) with an axis of + 100-105 degrees and no P waves. There are QS complexes in leads I, aVL and V_2 , and QR's in V_1 . Figure 7 B shows also an ugly RBBB with LPH, a similar axis, questionable PVC's and QS complexes in leads I, aVL and V_3 . Another trace was relatively normal. Figure 8 (K 7, Na 130, CO_2 < 10 meq/L) reveals an almost regular tachycardia, rate 145, probably a SVT (reentry) with RBBB aberration. P waves are not discernible but may be fused with T's (leads I, aVF). Slight ST depression is present in leads II, V_{3-6} and T waves are peaked in V_{3-6} . These traces are compatible with moderate to far-advanced hyperkalemia.

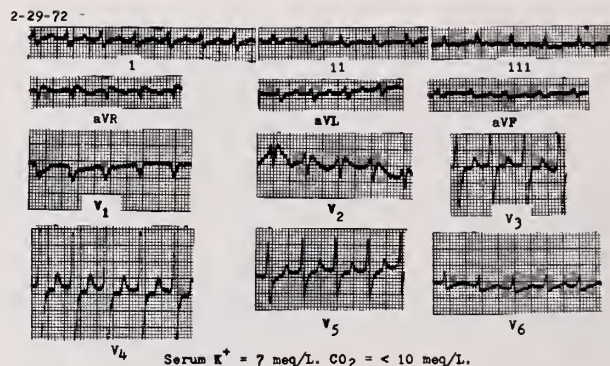


Figure 8. K = 7 meq/L. SVT (? AV nodal reentry) with RBBB aberration. Peaked T waves.

Discussion

Table I lists the electrophysiological effects of hyperkalemia. Table II summarizes electrocardiographic findings and cardiac arrhythmias for various stages and approximate serum levels of hyperkalemia.

The degree of hyperkalemia correlates fairly well with the QRS width, automaticity of the ventricles, ventricular rate (inversely proportional), heart block and severity of arrhythmias. However, the rapidity of potassium change, spontaneous versus "therapeutic" hyperkalemia, antiarrhythmic agents and the status of other electrolytes may influence the manifestations. Acidosis, hyponatremia and hypermagnesemia potentiate or mimic, while saline, bicarbonate, calcium, glucose and insulin IV may reverse the electrocardiographic abnormalities. Digitalis, pericarditis, bundle branch block, LVH with strain and MI may alter or obscure the typical patterns. Differential diagnosis involves several conditions because of the broad QRS complexes, prominent T waves, sinoventricular conduction and complex cardiac arrhythmias. Uremia classically presents hyperkalemia plus hypocalcemia as the "tent in the desert" pattern, as the ST segment is long. Acute fluoride

TABLE I

Electrophysiology of Hyperkalemia

Phase 2 shorter (shortens Q-T interval and peaks T wave).

Phase 3 velocity increases. Shorter repolarization.

First increases (K 5-7 meq/L) and then decreases (>8 meq/L) excitability, conduction and automaticity.

Threshold potential same or augmented.

Augments vagal effects.

Decreases —

Resting Membrane Potential (less negative, hypopolarization)- decreased transmembrane gradient of K.

Action Potential (AP) amplitude and duration.

Upstroke velocity, dV/dt of Phase 0, rise of the AP, which slows conduction.

Refractory period (or increased).

Depresses the rate and slope of Phase 4 diastolic depolarization, and thus automaticity, by increasing the membrane conductance of K.

Depresses and slows conduction in atrial and ventricular muscle, but has less effect on the specialized conduction tissues - sinoatrial node (least), internodal tracts, atrioventricular (AV) node, His bundle, Purkinje tissues.

Conduction may be accelerated in mild hyperkalemia (6-6.5 meq/L).

Increases the artificial pacing threshold (ventricular excitability threshold).

Increases —

Stimulus to A interval.

H - V interval.

H complex may be wide, slurred, of decreased amplitude and the H may precede the QRS complex.

Continued passage of impulses down the Purkinje network after asystole.

Altered intramural activation.

intoxication can cause peaked T waves suggesting hyperkalemia and refractory ventricular fibrillation. Moderate hyperkalemia (K 6.9 meq/L) can enhance the electrophysiological effects of disopyramide (P abnormality, wide bizarre QRS, second degree AV block and hypotension) and quinidine. Hyperkalemia may be diagnosed even in the presence of ventricular pacing and atrial fibrillation by the loss of atrial activity and the increased duration of the paced QRS complexes. The hyperkalemia of drugs such as potassium, chronic heparin, indomethacin, addisonian crises, propranolol (depresses intraven-

tricular pacemakers and AV conduction) and digoxin (can cause AV block in the elderly even with non-toxic levels) can be serious. Large doses of digitalis (near lethal serum K levels) may simulate a hyperkalemic aberration with wide QRS complexes, but markedly shortened QT interval. Moderate hyperkalemia can precipitate acute heart block with a failing ventricular pacemaker and arrest (in acute MI and hyporeninemic hypoaldosteronism), can block conduction through the accessory pathway (Kent) and abolish the delta wave in the Wolff-Parkinson-White syndrome (Segers 1944), and can ra-

TABLE II

Electrocardiographic Findings in Hyperkalemia

Mild Serum K 5.5-6.5 meq/L	<p>Tall, peaked, tented, symmetrical T waves with a narrow base. "Tented T's of toxicity"</p> <p>Slight P-R interval shortening</p> <p>These T wave changes may normalize or make upright the inverted T's of the Juvenile T Pattern, primary T's, digitalis T's and those of LVH.</p> <p>Bundle branch block, hemiblock, pseudoMI patterns possible.</p>
Moderate Serum K 6.5-7.5 meq/L	<p>P waves broad, low amplitude (slow atrial conduction)</p> <p>P-R interval lengthens. First degree AV block.</p> <p>QRS complex widens diffusely - intraventricular blocks</p> <p>Hemiblocks</p> <p>Q-T interval may shorten or prolong slightly</p> <p>Failure of cardiac capture by artificial pacemaker</p>
Advanced Serum K 7.5-8.5 meq/L	<p>P waves flat and broad</p> <p>Sinus pacemaker may shift</p> <p>P-R interval (P width and P-R segment) lengthens</p> <p>First degree and perhaps Wenckebach second degree AV blocks</p> <p>R waves decrease in amplitude; S waves increase in depth and width.</p> <p>Axis shifts</p> <p>Marked diffuse intraventricular blocks. Posterior and superior terminal QRS forces are accentuated.</p> <p>RBBB. LBBB. Bifascicular and trifascicular blocks</p> <p>ST segment elevated or depressed or is nonidentifiable.</p> <p>Arrhythmias. PVC</p>
Far-Advanced Serum K 8.5-10 meq/L or greater	<p>P waves disappear</p> <p>Sinoatrial block - Types I, II. Sinoatrial arrest</p> <p>Shift of atrial pacemaker to the AV node, His bundle</p> <p>Sinoventricular conduction</p> <p>AV block. - first degree, second (Types I, II), advanced, complete Heart block is rare or impossible to diagnose.</p> <p>QRS complexes - decomposed; wide with various intraventricular blocks; prominent S waves.</p> <p>Large, bizarre irregular biphasic "sine waves"</p> <p>PseudoMI patterns - loss of R waves, reversible Q's in V₁₋₃, diaphragmatic.</p> <p>Q waves, rare.</p> <p>ST segments - disappear; straight line from nadir of S wave to peak of T wave. Elevated and coved with inverted T - Injury Current.</p> <p>Q-T interval lengthens</p> <p>T waves may lose their peaked and narrowed appearance.</p> <p>U waves become smaller or disappear.</p> <p>Arrhythmias - sinus bradycardia, tachycardia, sinus arrhythmia.</p> <p>SVT, Atrial fibrillation and flutter (may be suppressed when K > 7 meq/L).</p> <p>Junctional - accelerated, escape. Low atrial.</p> <p>Ventricular - escape rhythms, VT, slow VT, flutter, fibrillation (reentry, un- even recovery).</p> <p>Ectopy</p> <p>Ventricular asystole (nonexcitable, failure to conduct and escape).</p> <p>AV dissociation, Exit block. Concealed conduction.</p> <p>2:1 electrical alternans. - mainly ST and T.</p> <p>Escape-capture bigeminy. Agonal rhythms.</p> <p>Conversion of chronic atrial fibrillation to normal sinus rhythm-K 8.9 meq/L.</p> <p>Failure of artificial pacemaker to capture.</p> <p>Death. Sudden death in a patient with a pacemaker and hyperkalemia.</p>

rely restore ventricular pacing response to an electrical pacemaker (decreases a high threshold and regains capture) *

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URETERAL OBSTRUCTION IN A
TRANSPLANTED KIDNEY
RENAL DYNAMIC STUDY
(^{99m}Tc-DTPA)

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Case Summary

A 25-year old male was admitted on January 18, 1981 for a renal transplant. He has history of urological problems before age six, when a right nephrectomy was performed due to nephrolithiasis. Since then, he had been submitted to several operations including a cystostomy at age nine, a left cutaneous ureterostomy at age 12, and a left nephrectomy at age 25, as preparation for kidney transplantation. He had been on hemodialysis since age 18.

On January 21, 1981, the patient underwent kidney transplantation. After implantation of the ureter, the renal pelvis and the ureter were seen to be dilated. An indwelling catheter was left in the bladder which drained scanty cherry red urine. Due to the poor urine output during the first two post-operative hours a renal dynamic study (^{99m}Tc-Diethylene triamine penta-acetic acid (DTPA) was performed (Fig. 1).

In view of the findings, reimplantation of the ureter was performed. Due to the presence of a fibrotic bladder, with a maximal volume of 20 ml, a catheter was placed draining the renal pelvis to the skin. In the first hour after the second procedure urine volume was 500 ml. The subsequent post-operative course was satisfactory. A second ^{99m}Tc-DTPA study (Fig. 2) confirmed the adequacy of the procedure.

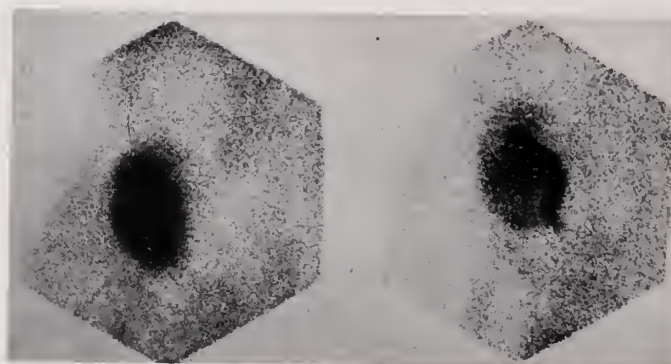


Figure 1: Views of renal dynamic study (^{99m}Tc-DTPA) 5 minutes and 60 minutes after injection, 3 hours after operation. They demonstrate retention of the material in the collecting system indicative of ureteral obstruction.

Comments

Due to the immunosuppressive therapy to which these patients are submitted most of the complications found after renal transplantation are infectious. There may also occur other problems including rejection, obstructive uropathy, lymphocele formation and vascular stenosis.

Radionuclide studies are very useful for monitoring of transplanted patients and the detection of most of the mentioned complications (1). The-

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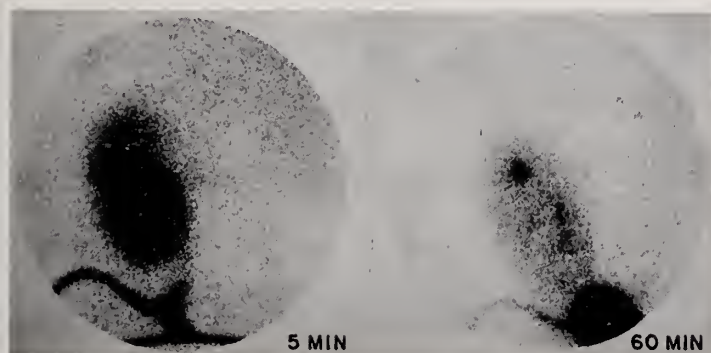


Figure 2: Views at same time intervals, 19 days after reimplantation of the ureter show adequate drainage into the bladder and through a catheter, externally.

se studies may be performed without difficulty during the immediate post-operative period and serially thereafter if necessary.

The renal dynamic study is performed with $^{99m}\text{Tc-DTPA}$, a chelate which is highly stable following intravenous injection and has a plasmatic half life of 70 minutes. Ninety five percent of it is excreted by glomerular filtration in 24 hours (2).

The study consists of a rapid bolus injection of $^{99m}\text{Tc-DTPA}$, after which serial images are

taken during a 30 to 120 minutes period. This permits evaluation of renal perfusion, regional glomerular function, gross renal structure and structure and function of the collecting system (3).

The low dose of radiation produced by the material, its excellent imaging qualities and absence of untoward reactions are advantageous over the compounds, including x-ray contrast agents.

Furosemide has been recently introduced for the differentiation of stasis in dilated portions of the collecting system from actual obstruction during renal studies with orthoiodohippurate or $^{99m}\text{Tc-DTPA}$ (4).

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LA FISIATRIA Y EL FISIATRA

Herman J. Flax, MD, FACP

La Fisiatría se enorgullece en promulgar la práctica terapéutica de trabajo en equipo en la medicina moderna. Howard A. Rusk creó este concepto, después de la Segunda Guerra Mundial, al utilizar las diferentes profesiones aliadas a la medicina para servir a pacientes severamente incapacitados. La muy repetida definición inicial de rehabilitación como la "tercera fase de la medicina" luego del diagnóstico y tratamiento, fue, afortunadamente, muy pronto substituída por el concepto moderno de un programa continuo de rehabilitación siguiendo la secuencia de un buen cuidado médico. No obstante, el programa original fue rápidamente copiado por otras especialidades para beneficio de sus pacientes debido a su eminente triunfo. Nadie puede negarle el mérito de este precedente a Medicina Física y Rehabilitación.

Subsiguientemente cayó en boga la expresión de que la fisiatría es la práctica holística de la medicina. "Holística" viene de "holismo" que se origina de la palabra griega "holos" que significa "un todo". Quien usó este término por primera vez en medicina de rehabilitación debe haber vislumbrado que el paciente se beneficia más recibiendo terapias multidisciplinarias de diferentes personas que si recibiera una sola terapia o quizás dos. Por encima de todo, debe haber motivación. Motivación de parte del paciente y motivación de parte del personal es un ingrediente "sine qua non" en la práctica de la rehabilitación. Un paciente que no está motivado, no se rehabilita, no importa las competencias del personal que lo trate.

Con experiencia, el fisiatra logra reconocer síntomas clásicos de enfermedades neuromusculoesqueletales que lo ayuda al diagnóstico. Ejemplo de esto, son los patrones de marcha observados en hemipléjicos y en enfermos de Parkinson. La posición antálgica causada por la irradiación ciática es tan diagnóstica de disco lumbar herniado que excluye la necesidad de otras pruebas dolorosas para el paciente. Existen, por cierto, millares de señales que agudizan nuestra perspicacia diagnóstica porque son diferentes a lo normal. El fisiatra astuto debe reconocer las variaciones de lo normal y no confundirlas con enfermedad. En la misma medida en que si usted escucha al paciente, éste le dará el diagnóstico, un examen físico cuidadoso lo protegerá de los pecados de omisión que invariablemente lo perseguirán eternamente. El médico no debe nunca escatimar el tiempo que se requiera para alcanzar el diagnóstico de "ninguna enfermedad". De hecho, éste es el diagnóstico más difícil de hacer, pero es precisamente el conocimiento de lo normal lo que facilita el reconocimiento de lo anormal. Además, estas variaciones sutiles de los llamados patrones normales, son testimonio de la plasticidad del cerebro y los músculos y ayudan a entender no solo la fisiología sino también la patología y pronóstico de la enfermedad. Recuerdenlas, porque estas excepciones a nuestro actual cúmulo de conocimientos son los fundamentos para futuros descubrimientos médicos.

Ahora, una vez hecho el diagnóstico, se procede con el tratamiento. En Medicina Física y Rehabilitación no hay indicaciones específicas como las conocemos en medicina. Básicamente, tratamos problemas, no enfermedades. La mayoría de los pacientes no están interesados en el diagnóstico siempre y cuando se le alivien los síntomas. Un diagnós-

tico correcto es importante para el fisiatra en una forma negativa, para evitar la prescripción de terapias inútiles. Hay algunos que creen que ayudar a la gente es más importante que diagnosticar una enfermedad. Esto es, apenas, una excusa idónea para que el buen médico prescriba e indudablemente no es argumento para combatir un pleito por mala práctica médica; y, debo añadir, el profesionalismo es una excusa pobre para prescribir terapia innecesaria. Debemos evitar esta pobre práctica de la medicina a todo costo.

El fisiatra, por otro lado, debe evaluar y tratar juiciosamente una gran clientela con síntomas neuróticos. Debemos aprender a vivir con estos pacientes, a controlar nuestras emociones personales, comprender que para ellos, sus síntomas son reales e importantes y entender la razón para la consulta. La mayoría de la gente son, usualmente, físicamente cobardes. La mera explicación de la causa y el asegurarles que el "espantoso" complejo de síntomas es benigno, es todo lo que se necesita para lograr una cura milagrosa.

La Fisiatría es la especialidad del fisiatra, pero la rehabilitación concierne a todos los programas médicos. Nombre la enfermedad y la rehabilitación se convierte en un diente importante de la rueda terapéutica. Con el adelanto en destrezas médicas y quirúrgicas, los pacientes ya no desaparecen

y sus vidas se prolongan a pesar de sus incapacidades. Hay mucho que podemos hacer para enseñar a este paciente a ser mucho más autosuficiente, y como dijo George Morris Piersol, de la Universidad de Pennsylvania, muy elocuentemente en una ocasión, "No solamente para añadir años a la vida, sino vida a los años". Según el promedio de vida lentamente se acerca a la marca del siglo, el número de pacientes con enfermedades crónicas, debilitantes, degenerativas e incapacitantes aumenta considerablemente. La Organización Mundial de la Salud conservadoramente estima que el 10 por ciento completo de la población mundial requiere rehabilitación urgentemente. Hasta que se conquisten estas dolencias y se eviten los problemas genéticos, estos números seguirán multiplicándose. Es por esto, que yo soy optimista sobre el futuro de la fisiatría y del fisiatra, porque la demanda por servicios de rehabilitación continuará aumentando año tras año. Lo que era "de jure" en 1947* es "de facto" en 1980. Hoy en día, la fisiatría se ha convertido en parte integral de la práctica médica; y mientras la gente viva y sean afligidos por enfermedades incapacitantes, la práctica de Medicina Física y Rehabilitación florecerá y el fisiatra persistirá.

* - Año en que se fundó "The American Board of Physical Medicine and Rehabilitation".

PHYSICAL MEDICINE AND REHABILITATION

Arturo Arche Matta, MD

1. La mayoría de los pacientes con dolor crónico se acompañan de:
 - a. histeria
 - b. depresión
 - c. ansiedad
 - d. psicosis
2. El nervio envuelto en el síndrome del túnel carpiano es:
 - a. músculo cutáneo
 - b. radial
 - c. mediano
 - d. ulnar
3. La complicación más frecuente de la estimulación nerviosa transcutánea (TENS) es:
 - a. shock eléctrico
 - b. rash en la piel
 - c. aumento en el requerimiento de analgésico
 - d. el paciente tiene que estar quieto mientras es tratado
4. Los efectos fisiológicos del calor terapéutico incluye todos excepto:
 - a. aumento en la temperatura tisular
 - b. aumento en el metabolismo
 - c. aumento en la vasoconstricción
 - d. aumento en la circulación sanguínea
5. El tratamiento de elección para el manejo de la vejiga en pacientes de trauma a la médula espinal es:
 - a. drenaje continuo con cateter tipo Foley.
 - b. cistostomía suprapúbica
 - c. cateterismo intermitente
 - d. drenaje continuo con cateter tipo gibbon
6. En qué tipo de contracción el músculo mantiene su longitud:
 - a. isokimética
 - b. isoto
 - c. isométrica
 - d. ninguna de ellas
7. Los objetivos de los ejercicios pueden ser terapéuticos o profilácticos; incluyen todos excepto:
 - a. aumentar el arco de movimiento
 - b. fortalecer músculos débiles
 - c. aumentar el grado de contractura
 - d. mejorar el balance y la coordinación
8. El "Rotator Cuff" está compuesto por los siguientes músculos:
 - a. músculos supraespinosos, infraespinosos "Teres mayor" subescapular
 - b. músculos supraespinosos, infraespinosos, "Teres mayor" y "teres minor"
 - c. músculos supraespinosos, sub-escapular, "Teres mayor" y "Teres minor"
 - d. músculos supraespinosos, subescapular infraespinoso y "teres minor"

9. Pareo:

Músculo	Enervación Segmentaria
a. Quadriceps	1. L ₅ - S ₂
b. Ilio-psoas	2. L ₄ - S ₁
c. Gluteo médico	3. L ₂ - S ₄
d. Gluteo máximo	
e. Hamstring	

10. Pareo:

Músculo	Nervio
a. Supraespinatus	1. Torácico largo
b. Deltoide	2. Dorsal escapular
c. Romboides	3. Supra escapular
d. Serrato Anterior	4. Axilar
e. Infraespinatus	5. Músculo cutáneo
f. Coraco braquial	

UN CASO COMPLICADO DE DIARREA

Angel Olazábal, MD
Hospital de Veteranos, San Juan, P. R.

Un hombre de 50 años se presenta con la queja de diarreas por cinco días. Las diarreas ocurren durante la noche y de día. El es diabético y se queja de adormecimientos de los pies y las manos. Recibió un antibiótico (no sabe el nombre) una semana antes del comienzo de la diarrea por una infección de garganta mientras viajaba en México. Había perdido 10 libras el mes antes del comienzo de las diarreas y cinco libras adicionales en la última semana. Se queja de sentirse mareado y débil al pararse. Admite que estuvo en alcoholicos anónimos, que anteriormente tuvo pancreatitis y que lo operaron hace un año de un "quiste". Al final del examen él pregunta si hay alguna relación entre las diarreas y ser homosexual.

1. ¿Cuáles de las siguientes pruebas de laboratorio mandaría?

- a. concentración sérica de glucosa
- b. sangre oculta en la excreta
- c. determinación cualitativa de grasa en la excreta (prueba de Sudan)
- d. examen microscópico de una muestra de excreta teñida con methylene blue

2. ¿Cree usted necesario algunas de las siguientes pruebas?

- a. cultivo de la excreta para patógeno
- b. examinación de la excreta para parásitos
- c. determinación de la concentración de magnesio y fosfato en la excreta
- d. microscopía electrónica de rastreo (scanning) de una muestra fecal

3. Si le administra fluidos y el paciente persiste sintiéndose mareado al pararse, ¿cuáles de las siguientes explicaciones se deben considerar? (La presión es 100/70 acostado y 75/60 de pie).

- a. hypocalcemia
- b. hiporeninemia
- c. neuropatía por amiloidosis
- d. sepsis

4. Al paciente se le hace una sigmoidoscopia y se examinan los 25 cm. distales de intestino. Si la mucosa se nota friable y edematosa, ¿cuáles de las siguientes alternativas haría? (Las pruebas de coagulación y el número y la función de las plaquetas son normales).

- a. nada más
- b. biopsia a 25 cm. con las pinzas de biopsias.
- c. biopsia a menos de 8 cm. con las pinzas de biopsias.
- d. Un cultivo de la mucosa rectal para Neisseria gonorrhea.
- e. Examinar una biopsia rectal para huevos de Schistosoma mansoni.

5. Si la apariencia de la mucosa es normal hasta 25 cm, ¿cuáles de las siguientes alternativas diagnósticas están descartadas?

- a. colitis ulcerativas
- b. colitis de Crohn
- c. colitis pseudomembranosa
- d. diverticulitis
- e. amiloidosis infiltrando el recto

(Contestaciones en página 119)

ABSTRACTOS DE LITERATURA MEDICA

JUVENILE MUSCULAR ATROPHY LOCALIZED TO ARMS

Naunihal Singh, MD, Kuldip K. Sachdev, A. K. Susheela, PhD, Archives of Neurology, Vol. 37: 297-299, 1980.

24 pacientes de la India se encontraron con atrofia muscular juvenil, localizada en las extremidades superiores. La condición afecta característicamente a hombres jóvenes y no es familiar. La atrofia está limitada a las manos y músculos del antebrazo con progresión lenta por dos o tres años que luego se hace estacionaria. La condición es asociada con movimientos "tremor like" fuera de proporción con la debilidad. Examen de especímenes de biopsia de músculos demuestran atrofia de fibras Tipo 2. El síndrome, cuya causa aún no se conoce, es benigno y autolimitante. A diferencia de la enfermedad de neurona motora, es distal en las extremidades superiores. También en esto se diferencia a la enfermedad de Kugelberg Welander. Los desgastes musculares asimétricos son precedidos por enfermedades febriles en algunos pacientes y sugieren poliomielitis atípica o enfermedad viral.

(Sometido por Edgar Baucage, MD, VAH)

ESTUDIOS SERIADOS DE LA CONDUCCION DEL NERVIIO FRENICO EN CANDIDATOS PARA "PACING DIAFRAGMS

J. Llebberman, M. D., Guy Corkill, M. D., M. N. Nayak and B. French, M. D., R. Taylor, MD, Arch. P. M. & R. 61: 528-531, 1980.

Estudios Seriadados de la Conducción del Nervio Frénico en 3 pacientes con lesión cervical alta del cordón espinal han demostrado un patrón de funcionamiento que cambian con el tiempo. El nervio puede responder inicialmente y puede convertirse sin repuesta. Solo aparecieron repuesta en días tardíos antes de hacer una decisión final sobre la viabilidad del nervio frénico antes de "Diaphragma Pacing". Serie de estudios deben hacerse por lo menos 6 semanas preoperatorio en la repuesta inicial del nervio y por lo menos 2 años post operatorio en nervios sin repuestas o aquellos con cambios funcionales de patrones funcionales.

(Sometido por E. Baucage, MD, VAH)

CIRCULORESPIRATORY RESPONSE TO PROLONGED TREADMILL AND BYCICLE EXERCISE

Deutsch, D. T., Knowlton, R. G.: Arch. Phys. Med. Rehabil. 61: 298-303, 1980.

Se estudió la respuesta circulorespiración de un grupo de 9 (nueve) hombres no entrenados en ejercicios en treadmill (correa sin fin) y bicicleta por un período de 60 minutos. Se determinó la variabilidad de la actividad aeróbica prolongada y el efecto de extender la duración del ejercicio. Se observó la variación en la respuesta cardiorespiratoria dependiente del modo de ejercicio con igual gasto de energía. No hubo diferencias significativas entre los modos de ejercicios en el mejoramiento de presión

arterial, gasto cardíaco, etc. El aumento de tiempo de ejercicio indicó una variabilidad en respuesta cardiorespiratoria de ambos tipos de ejercicios encontrando que el treadmill impone menor carga al sistema cardiorespiratorio.

(Sometido por F. W. López, MD, VAH)

THE USES OF EXERCISE STRESS TESTING

Wenger, N. K., *Emergency Medicine*, 1980, Vol. 12, Number 21, pp 24-23

Artículo que no es un estudio en sí sino una disertación sobre lo referente a la prueba de esfuerzo en el presente.

Comienza por una descripción del equipo de prueba y de seguridad. Luego nos describe los protocolos y la forma de reportar los resultados. Continúa por describir las indicaciones y precauciones a saber, en la prueba de esfuerzo. Específicamente cubre al paciente que ha sufrido un infarto y es candidato para un programa de rehabilitación cardíaca. Nos demuestra la forma en que la prueba de esfuerzo nos da una idea del pronóstico del paciente con insuficiencia coronaria. Incluye casos reales y trazados electrocardiográficos típicos.

(Sometido por José A. Arabía, MD, VAH)

PSYCHOSOCIAL DISABILITY IN PHYSICALLY RESTORED LONG-TERM STROKE SURVIVORS

Labi, M. L. C., Phillips, T. F., Gresham, G. E.: *Arch Phys Med Rehabil* 61: 561-565, 1980.

Tres parámetros de función social (sociali-

zación en el hogar, socialización fuera del hogar y pasatiempos e intereses) se analizaron para determinar la reintegración de los supervivientes de una apoplejía completada y documentada, que han logrado unos niveles satisfactorios de función física medidos por el sistema Kenny. Una proporción significativa de supervivientes manifestaron incapacidad social, a pesar de una recuperación física completa. La mayor parte de la incapacidad no puede atribuirse a edad, incapacidad física o déficits neurológicos específicos. La distribución de incapacidades funcionales documentadas sugiere que factores psicosociales, así como los déficits orgánicos, son determinantes muy importantes.

(Sometido por M. Berrios, VAH)

MUSCULAR STRENGTH AS INDEX OF RESPONSE TO THERAPY IN CHILDHOOD DERMATOMYOSITIS

Resnick, J. N., Mundale, M. O., Mammel, M., Kotte, F. J.: *Arch Phys Med Rehab*. 62: 12-19, 1981.

La dermatomiositis, enfermedad inflamatoria de etiología desconocida, causa debilidad y atrofia simétrica difusa, dolor muscular, endurecimiento muscular, y la tendencia a desarrollar contracturas. La enfermedad puede seguir un curso prolongado cuyo mejor manejo consiste en el uso de esteroides y la regulación de la actividad física si hay un criterio objetivo para determinar la extensión del involucramiento clínico. En 6 niños con dermatomiositis, la fuerza muscular cuantitativa se comparó con la evaluación clínica del estado de la enfermedad, niveles de enzimas séricas y otras medidas de laboratorio para inflamación sistémica. La evaluación cuantitativa de la fuerza de los flexores plantares por el método de Basley o la fuerza de agarre por el método de Mundale indicaron que la fuerza muscular supuso un criterio mejor para el estado clínico del paciente que cualquier prueba de laboratorio estu-

todo de Mundale indicaron que la fuerza muscular supuso un criterio mejor para el estado clínico del paciente que cualquier prueba de laboratorio estu-

diada. En la dermatomiositis, la inflamación es igual en los músculos distales que en proximales cuando se prueban cuantitativamente. Estas pruebas, cuando son utilizadas junto a niveles enzimáticos y la evaluación clínica permiten un manejo más efectivo de la dermatomiositis en niños.

(Sometido por M. Berríos, MD, VAH)

TRAUMATIC HEAD INJURY: RESTLESSNESS AND AGITATION AS PROGNOSTICATORS OF PHYSICAL AND PHYSIOLOGIC IMPROVEMENT IN PATIENTS

Reyes, R. L., Heller, D., Battacharyya, A. K. - *Arch. Phys Med. Rehabil.* 62: 20-23, 1981.

87 pacientes con lesiones traumáticas de cráneo fueron evaluadas desde su admisión hasta después de haber sido dados de alta por un período de 5 años. Usando criterios objetivos se evaluó su nivel de actividad post-traumático (NAPT) a la admisión y se comparó con su estado general y cognitivo al ser dados de alta durante el seguimiento. La mayoría de los pacientes regresaron a la comunidad, sin embargo, los pacientes agitados demostraron tendencia a desarrollar problemas psicológicos. Los pacientes inquietos y agitados tuvieron mejoramiento físico funcional el cual se relacionó inversamente relacionado con el ajuste psicológico. Los pacientes con actividad motora apropiada y los inquietos mostraron la mayor tendencia a mejorar cognitivamente.

(Sometido por Jesús Maldonado, MD, VAH)

Medi-Quiz - Physical Medicine and Rehabilitation

RESPUESTAS

1. B
2. C
3. B
4. C
5. C
6. C
7. C
8. D
9. a-3
b-3
c-2
d-1
e-1
10. a-3
b-4
c-2
d-1
e-3
f-5

CONTESTACIONES A MEDI-QUIZ

Un Caso Complicado de Diarrea

1. Todas las pruebas están indicadas. El paciente es diabético. Hay que descartar lesiones del tubo digestivo asociadas con pérdida de sangre en la excreta. El examen de Sudan ayuda a evaluar para steatorrea significativa (presente en problemas de malabsorción y maldigestión. El paciente pudiera tener insuficiencia pancreática). El examen de methylene blue demuestra la presencia de leucocitos en la excreta (presentes en condiciones de colitis).

2. Las primeras dos opciones están claramente indicadas para descartar infección intestinal por bacterias del tipo de Salmonella y Shigella y parásitos como Entamoeba histolítica y Giardia lamblia. Las determinaciones de electrolitos como sodio, potasio, cloruro y la determinación de la osmolaridad pueden estar indicadas en ciertos casos de diarrea para determinar si la diarrea es de tipo osmolar o secretora. Las alternativas c y d no están claramente indicadas.

3. Las respuestas b, c, y d explicarían la hipotensión. Diabéticos con neuropatías periféricas pueden también tener neuropatías viscerales. También pueden tener hiporeninemia e hipoaldosterismo y poco aumento del nivel sérico de renina y aldosterona con cambios posturales. Amiloidosis con neuropatía puede asociarse con hipotensión postural. Amiloidosis envolviendo el tracto digestivo se puede considerar en el paciente ya que tie-

ne diarrea, pérdida de peso, cambios posturales de la presión. Sepsis se debe considerar en pacientes con diarreas e hipotensión.

4. Cuando se hacen biopsias por sigmoidoscopia con las pinzas de biopsia, se recomienda que se tomen a un nivel por debajo de la reflexión peritoneal que usualmente ocurre de 8 a 10 cm. proximal al ano. Infección rectal por gonorrea puede ocurrir en homosexuales. En personas que viven en Puerto Rico estaría indicado tomar una biopsia rectal para detectar una posible infección por Schistosoma.

5. Ninguna se descarta con certeza. Quizás la menos probable sería una colitis ulcerativa, pero a veces la actividad se demuestra en el examen histológico únicamente. Colitis de Crohn no envuelve el recto en muchos pacientes. Las lesiones de colitis pseudomembranosa (que consisten de placas de material fibrinoide, necrótico, e inflamatorio y que cuando se remueven con el aplicador de algodón se nota una mucosa ulcerada) pueden ocurrir más proximalmente en el colon y los últimos 25 cm. estar libres de lesiones. La lesión de diverticulitis con frecuencia está a más de 25cm del ano. Cuando amiloidosis infiltra el tracto gastrointestinal la apariencia endoscópica puede ser normal y el diagnóstico depende de la apariencia histológica y la demostración de amiloide con tintes especiales como el Congo Red.

NOTICIAS

PEDIATRIC DERMATOLOGY SEMINAR IX - Primary Notice

The 9th annual Pediatric Dermatology Seminar will convene at the new Carillon Beach Hotel, Miami Beach, Florida, February 25th-28th, 1982. Guest Speakers will include: Richard Dobson, Nancy Esterly, Yehudi Feldman, Sidney Hurwitz, Lowell Goldsmith, Guinter Kahn, Arthur Norins, etc. The seminar fee remains at \$190. A two week post-seminar tour to East Africa is planned. Nairobi, Kenya, Lake Victoria, renowned game reserves and safaris are on the itinerary. The cost will be approximately \$2000 per person.

For information contact: Guinter Kahn, MD, (305/652-8600) 16800 NW 2 Ave., Miami, Florida, 33169.

AMA NEWS:

BREAST CANCER SCREENING FOR YOUNGER WOMEN ENDORSED

CHICAGO — Screening of younger women for breast cancer pays off in detecting cancers early while treatment still offers hope of success, says a report in the March 13 Journal of the American Medical Association.

Breast cancer screening has been recommended for all women past the age of 50. But there has been difference of opinion as to whether routine mass screening of women 35 to 50 was worthwhile in terms of cancers discovered in relation to numbers screened and cost. Screening of younger women no longer is recommended in many centers.

Several years ago the American Cancer Society and the National Cancer Institute funded the development of breast cancer detection demonstration projects to learn more about the effectiveness of mass screening programs. The first report from one of these projects at the University of Louisville School of Medicine — calls attention this week to the value of screening women under 50 as well as those over that age.

The Louisville group reports on a five-year screening experience for 10,128 women at the Louisville Breast Cancer Detection Demonstration Project. The screening disclosed 163 breast cancers in women aged 35 to 74 years. Thirty-four percent of those with cancer were younger than 50 years. In 69 percent of the total of cancer patients the disease had not yet begun to spread through the rest of the body at the time of diagnosis.

Of the 10,128 patients, 5,280 were between the ages of 35 and 50 years. In this group 38 cancers were detected in 37 patients through the screening program. Thus, one in each 140 younger women screened were found to have breast cancer.

Project Chief Kirby I. Bland, M. D., concludes: "The Project has conferred screening benefit to women younger than 50 years as well as those in an older age."

SURVIVAL RATE IMPROVING FOR SYSTEMIC LUPUS ERYTHEMATOSUS

CHICAGO — Medical science is learning more about a particularly stubborn and uncomfortable disease — systemic lupus erythematosus — and

ly in recent years.

Systemic lupus erythematosus (SLE) is a chronic, inflammatory disease of unknown cause affecting skin, joints, kidneys, nervous system, and often other organs of the body. The most obvious sign is a persistent skin rash with a classic butterfly pattern.

The disease strikes about one person in each 1,000 and is five to 10 times more common among females than males.

In a report in the March 6 Journal of the American Medical Association, a California research group relate experience in treating 609 patients with SLE, with a follow-up period of up to ten years.

The overall ten-year survival was 79 percent, said Edmund L. Dubois, M. D., of the University of California at Los Angeles School of Medicine. Male patients did worse than female patients. There was no basic difference in survival rates of blacks and whites.

One of the most serious results of SLE is kidney damage, and this was a factor in many of the fatal cases, Dr. Dubois found.

The survival rate of 79 percent was much improved over earlier results, and the California group credits improvement to closer follow-up, better nutritional status, and treatment begun at earlier stages of the disease.

"Our understanding of SLE has improved substantially over the last 30 years. While SLE initially was reported to have a 90 percent two-year mortality, more recent reports have shown much longer survival. This article represents the most cohesive group published to date. It represents the largest number ever reported by a private physician, with a follow-up report twice that of any other study," he said.

The disease progresses slowly. There is an average time lapse between first signs of the ailment and obtaining a diagnosis from the doctor of around four years.

"We believe that the socioeconomic problems of patients who attend the larger city or county hospital clinics affect survival significantly. Less optimal living conditions, poor nutrition, and inferior education lead to less reliable medication administration, missed clinic appointments, greater risk

of infection and presentation with more advanced disease," Dr. Dubois said.

BEER DRINKERS NOW ASSURED FREEDOM FROM CANCER FEAR

CHICAGO — Beer drinkers of the nation can now relax and enjoy moderate amounts of their foamy suds free of at least one health fear — cancer.

The nitrosamine content of both domestic and imported beer is for the most part below the level allowed by the U. S. Food and Drug Administration, says Stephanie C. Crocco, Ph. D., of the American Medical Association's Department of Foods and Nutrition.

The FDA permits only five parts per billion (equivalent to five cents in \$10 million) of nitrosamines in beer. Since January 1, 1980, the FDA has been monitoring the nitrosamine content of both domestic and imported beers. Although an occasional report appears that a given beer contains nitrosamines in excess of the allowed figure, beers usually do not contain such levels, Dr. Crocco reports.

Regulatory and industrial efforts also are aimed at holding down the amount of the substance found in barley malt used in beer production.

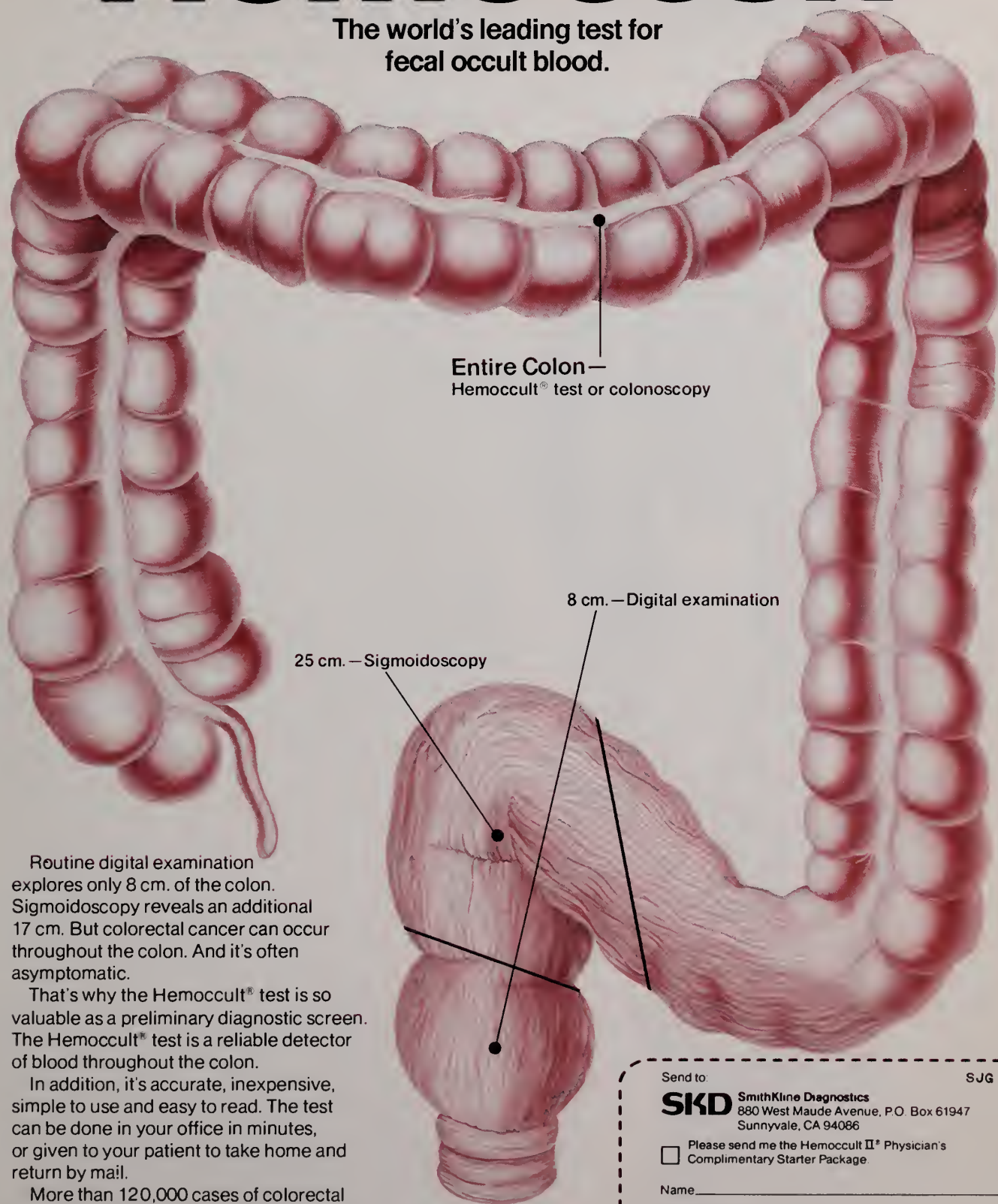
Nitrosamines are organic compounds containing nitrogen. Some of them are known to cause cancer in laboratory rats when given at much higher levels.

Of course, the report on beer in the JAMA is related only to nitrosamines and does not discuss health hazards of excessive drinking, including alcoholism and its concurrent health problems, and obesity.

The report is published in the March 6 Journal of the American Medical Association.

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WARNINGS:

Drug dependence: Empirin with Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral, narcotic-containing medications. Like other narcotic-containing medications, the drug is subject to the Federal Controlled Substances Act.

Use in ambulatory patients: Empirin with Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system (CNS) depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with Empirin with Codeine may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Use in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Empirin with Codeine should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS:

Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Empirin with Codeine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Allergic: Precautions should be taken in administering salicylates to persons with known allergies: patients with nasal polyps are more likely to be hypersensitive to aspirin.

Special risk patients: Empirin with Codeine should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture, peptic ulcer, or coagulation disorders.

ADVERSE REACTIONS: The most frequently observed adverse reactions to codeine include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, and pruritus.

The most frequently observed reactions to aspirin include headache, vertigo, ringing in the ears, mental confusion, drowsiness, sweating, thirst, nausea, and vomiting. Occasional patients experience gastric irritation and bleeding with aspirin. Some patients are unable to take salicylates without developing nausea and vomiting. Hypersensitivity may be manifested by a skin rash or even an anaphylactic reaction. With these exceptions, most of the side effects occur after repeated administration of large doses.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. Empirin with Codeine is given orally. The usual adult dose for Empirin with Codeine No. 2 and No. 3 is one or two tablets every four hours as required. The usual adult dose for Empirin with Codeine No. 4 is one tablet every four hours as required.

DRUG INTERACTIONS: The CNS depressant effects of Empirin with Codeine may be additive with that of other CNS depressants. See WARNINGS.



Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

ABDOMINAL STAB WOUNDS OFTEN HEAL WITHOUT SURGERY

CHICAGO — The street fight victim is rushed to the hospital emergency room with a stab wound in the abdomen.

Does the surgeon immediately take up scalpel and operate to find extent of damage and repair it? Only about half the time, in the approach followed at a New York City hospital.

In some half of the abdominal stab wound cases the preferred procedure is to wait. Admit the patient for careful observation and watch for signs that a vital organ is damaged and surgery is required, says Joseph R. Wilder, M. D., of the Hospital for Joint Diseases and Medical Center and Mt. Sinai School of Medicine, New York, in the June 27 Journal of the American Medical Association.

Often surgery is not required. No vital organ is seriously damaged, and the patient may be sent home after four or five days, Dr. Wilder says.

The New York surgeon points out that controversy still exists over the method of treatment of patients with stab wounds of the abdomen. Many surgeons continue to practice mandatory exploration in all such cases, he says. Dr. Wilder details his experiences with more than 400 stab wounds in 20 years, and concludes that surgery often is not needed.

All patients with abdominal stab wounds are treated as critically ill, regardless of their appearance, Dr. Wilder says. Sometimes surgery is required immediately, sometimes it can be postponed for a short time. And sometimes it is not needed. Careful observation of the patient and monitoring of vital functions is important in determining when to operate, he says. Even if the patient is intoxicated it is not always necessary to operate immediately.

"We believe that the results of our 20-year study of 403 stab wound patients justifies our confidence in continuing the policy of selective surgical intervention. The precipitous increase in the number of patients with stab wounds of the abdomen seen at our hospital is in keeping with the experience of most hospitals in the ghetto area," Dr. Wilder writes.

Ninety-four per cent of the stab wounds were homicidal, 4 per cent were accidental and 2 per cent were suicidal. In more than half of the cases injury was caused by known assailants, described as "friends". In 90 per cent of the cases the weapon was a blade, and in 7 percent an ice pick. Other weapons included fence posts, broken glass, coat hangers, screwdrivers and scissors.

Eighty per cent of the stab wound victims were addicts of heroin or similar drugs.

CURE OF SYPHILIS REQUIRES ONE TO TWO YEARS

CHICAGO — With the discovery of penicillin as a cure for many infections, syphilis — the scourge of mankind for centuries — became a curable disease.

But there still remains a backlog of syphilis that is passed among sexually active individuals, and many persons still become infected.

It is well known among the public that the disease is curable, and the primary question the patient asks the doctor is: How long will the cure take?

The answer is: One to two years, depending on the type of syphilis treated, says a report in the June 27 Journal of the American Medical Association.

Nicholas J. Fiumara, M. D., of the Massachusetts Department of Public Health and Boston University School of Medicine, studied 138 patients with primary syphilis and 161 patients with secondary syphilis to determine time required to cure the disease.

Dr. Fiumara found that the chancre sore will heal within a week or two, and the blood test will return to nonreactive state within 12 months for primary syphilis and 24 months for secondary syphilis.

Treatment in Dr. Fiumara's program was with penicillin G. benzathine. Those allergic to penicillin were treated with tetracycline hydrochloride.

Sometimes the blood test is favorable in less than a year, depending on how long the patient has had the disease, he said.

Of course, the cure does not protect against another infection, many individuals are treated for re-infections from additional exposures.

DROWNING VICTIMS SURVIVE LONGER IN COLD WATERS

CHICAGO — Emergency medicine experts had long assumed there was virtually no hope of recovery for the drowning victim under water more than five or six minutes.

In recent months, however, a number of reports have appeared in the medical literature of individuals who survived much longer immersion.

Doctors now know that the temperature of the water is the key factor. Icy cold water extends the survival period.

An American Medical Association publication, Archives of Internal Medicine, reports in the June issue on two patients who survived submersion in cold water. The report is by Kenneth F. MacDonnell, M. D., and colleagues, at St. Elizabeth's Hospital, Boston, Massachusetts.

A 23-year-old woman was a passenger in a car that plunged into the icy waters of the Charles River in Boston. Driver of the vehicle was extricated from the vehicle within a minute or two, but rescuers were not aware of the woman passenger until the auto was lifted from the water after 25 minutes.

Resuscitation was begun immediately and the victim was rushed to the hospital. The patient recovered gradually under treatment and went home after two weeks, mentally and physically normal.

A 27-year-old paralyzed man plunged with his motorized wheelchair into the Charles River and was under water for at least six minutes before rescue. He also recovered after a week in the hospital.

The cases illustrate that patients suffering prolonged submersion in cold water may be successfully resuscitated without permanent brain damage, Dr. MacDonnell says.

The extreme cold slows the metabolic rate of the brain, thus lessening brain damage from lack of oxygen while under water, he declares. The brain can survive much longer at low temperatures before permanent damage ensues. Body temperature of the woman auto accident victim was 84 degrees when she was brought to the hospital. Normal body temperature is 98.6 degrees.

In the United States there are an estimated 6,000 to 7,000 drownings each year.

NEW TREATMENT SHORTENS TIME FOR CURING TUBERCULOSIS

CHICAGO — An important recent advance in treatment of tuberculosis, shortening considerably the time required to cure the disease, is reported in the June issue of an American Medical Association publication.

It is now possible to treat new cases of tuberculosis in nine months, with a 97 per cent cure rate and a relapse rate of less than 1 per cent, says William W. Stead, M. D., of the Arkansas Department of Health, Little Rock.

The new method utilizes a combination of two potent drugs, isoniazid and rifampin, says Dr. Stead in Archives of Internal Medicine.

In addition to the shorter time lapse, it also is now possible to give the drugs less frequently. Cure rate is just as good when the schedule includes medication daily for only one month and then con-

tinuing at a modified dose for the other eight months, Dr. Stead says.

Those individuals who have relapsed from previous therapy and might be resistant to the dual drug treatment should be given other potent medications along with the two drugs.

For the past 20 years, the recommended duration of daily drug treatment for tuberculosis has been 18 to 24 months, Dr. Stead points out. Cooperation and compliance are difficult to maintain for the long period. The patient must continue to take drugs long after he feels well, and there is a strong tendency to stop too soon. Also, the drugs are expensive, and developing countries cannot afford such long treatment.

The two drugs must be used together to cope with natural occurrence of mutants of the tuberculosis organism that are resistant to any effective single drug, the Arkansas doctor says. The treatment program is now standard in both England and France, but is only recently coming into use in the United States. The two-drug regimen has been used on more than 1,000 patients in Arkansas in the past three years, with a 97 per cent success rate and less than 1 per cent relapse.

SECOND NATIONAL SEMINAR ON COMMUNITY CANCER CARE - September 25, 26 and 27, 1981, Hyatt Regency, Indianapolis, Indiana - Sponsored by the Clinical Oncology Center and the Graduate Medical Center at the Methodist Hospital of Indiana, Inc.

For information write: Office of Continuing Medical Education, Methodist Hospital of Indiana, Inc., 1604 N. Capitol Avenue, Indianapolis, Indiana, 46204.

FROM THE NATIONAL INSTITUTES OF HEALTH, CONSENSUS DEVELOPMENT - CONFERENCE SUMMARY - VOLUME 3 - NUMBER 7

CEA AS A CANCER MARKER

A Consensus Development Conference was held at the National Institutes of Health, September 29 - October 1, 1980, to address issues concerning the role of the carcino-embryonic antigen (CEA) as a marker in the management of cancer.

At NIH, Consensus Development Conferences bring together biomedical research scientists, practicing physicians, consumers, and others with special interest or knowledge, in an effort to reach general agreement on the scientific evaluation of a medical technology. That technology may be a drug, device, or laboratory, medical, or surgical procedure.

For this Consensus Conference, the members of the Panel were limited to biomedical and clinical investigators actively working in the field, clinically involved in patient care, and familiar with the technology under assessment. The Panel met following formal presentations and discussions to assess the issues based on the evidence presented. This summary is the result of the Panel's deliberations.

Introduction

Human neoplasms may produce and release into the circulation a variety of substances collectively referred to as *tumor markers*. The oncofetal antigens comprise one particular group of markers, of which the carcinoembryonic antigen (CEA) has been the most widely studied.

CEA is a glycoprotein of about 200,000 molecular size. It is expressed in significant amounts during embryonic life, especially by the large intestine, and postnatally by carcinomas arising from this site. CEA can be released by these tumors into the circulation to cause raised levels which may be measured by sensitive radioimmunoassay and related techniques. Such methods have, however, demonstrated that small amounts of CEA are also present in

the normal adult large intestine and in the circulation of healthy subjects.

Subsequent investigations have revealed that many epithelial-derived tumors at other sites may also express CEA and be associated with elevated circulating blood levels. Thus, it may be that the assay of plasma CEA has protean applications in oncology.

The Consensus Development Panel and members of the audience considered evidence to address the following questions:

1. Should CEA be used in cancer screening?
2. Is CEA helpful in cancer diagnosis?
3. What does CEA tell about the extent and outcome of cancer?
4. Is CEA helpful in monitoring cancer treatment?

Plasma CEA Levels in Health and Disease

Using the presently available radioimmunoassay, 2.5 ng/ml is stated to be the upper limit of normal for plasma CEA levels. Values in excess of 2.5 ng/ml may be found in association with cancers, in particular those of the gastrointestinal tract, pancreas, ovary, lung, and breast. Similarly raised CEA levels may, however, be detected in cigarette smokers, in patients with benign neoplasms, and in 15 to 20 percent of subjects with inflammatory disorders such as ulcerative colitis, Chron's disease, pancreatitis, liver disease, and pulmonary infections. Thus, raised plasma CEA values are not specific for cancer, although very high levels (for example, above 20 ng/ml) are highly suggestive of malignancy. It is important that serial assays of CEA be used in reaching a clinical judgment, and not any single determination. The panel believes that each laboratory performing CEA assays should establish its own "normal" range. The recommended upper level of "normal" (2.5 ng/ml) in the population requires additional evaluation. Values cited in this document are based on the only radioimmunoassay commercially available at the time of the conference, the Hoffman-La Roche assay. Other assay systems may give different results.

Conclusions and Recommendations

After listening to and discussing the evidence, the Panel reached the following conclusions:

1. Should CEA be used in Cancer Screening?

As indicated above, studies to date have revealed a major overlap in the distribution of plasma CEA values in subjects with inflammatory diseases and benign and malignant tumors of the gastrointestinal tract and of other sites, including breast, bronchus, urothelium, ovary, uterus, and cervix. Therefore, the plasma CEA assay does not possess the sensitivity (true-positive rate) or the specificity (true-negative rate) required to discriminate between localized malignant tumors and benign disorders.

Consequently, these data, together with the fact that raised CEA levels occur in smokers, vitiate the use of plasma CEA assays in the screening of an asymptomatic population to detect neoplastic disease. The use of CEA to assist with the surveillance of so-called high-risk groups, in whom CEA-producing tumors may develop, remains to be established.

2. Is CEA Helpful in Cancer Diagnosis?

Few prospective studies have been effected with the aim of determining whether the availability to clinicians of a plasma CEA result would help in confirming a suspected malignancy in symptomatic patients. In addition, the caveats with respect to cancer specificity which limit the CEA test's applicability for screening (namely, that raised levels occur with smoking, non-neoplastic diseases, and benign tumors) are also pertinent with respect to assisting in reaching a diagnosis in a symptomatic population.

Therefore, we cannot recommend, based on the presently available data, that CEA be used independently to establish a diagnosis of cancer. However, in a patient with symptoms, a grossly elevated value, greater than 5-10 times the upper limit of the reference normal range for that particular laboratory, should be considered strongly suggestive for the presence of cancer in that particular patient. In this

situation further diagnostic efforts to establish the presence or absence of cancer are indicated.

3. What Does CEA Tell About the Extent and Outcome of Cancer?

Many workers have shown that preoperative plasma CEA levels correlate with the clinical stage of disease in several tumor types. Patients with colorectal or, possibly, bronchial carcinomas whose preoperative CEA levels are at the lower end of the spectrum have better survival rates than patients whose levels are in excess of 10 ng/ml.

It should be remembered, moreover, that the correlation between increasing plasma CEA levels and progressive cancer is not always perfect and that a normal CEA cannot be taken as evidence of localized disease or remission. About 15 to 20 percent of patients with proved malignancies never have elevated plasma levels. Such false negatives may be related to the degree of tumor differentiation. Poorly differentiated colorectal carcinomas, for example, tend to be associated with a reduced proclivity for CEA expression and release.

On the basis of the available data, we recommend that a preoperative plasma CEA value be obtained in patients with either colorectal or bronchial carcinomas and be used as an adjunct to clinical and pathological staging methods.

4. Is CEA Helpful in Monitoring Cancer Treatment?

The regular and sequential assay of plasma CEA is the best presently available noninvasive technique for postoperative surveillance of patients to detect disseminated recurrence of colorectal cancer. As a monitor of colorectal cancer, CEA has been found to be elevated when residual disease is present or is clinically progressing. Following complete surgical removal of a colorectal malignancy, an elevated plasma CEA value should usually return to normal by 6 weeks. The failure to observe a reduction of a previously elevated preoperative CEA titer strongly indicates the presence of residual tumor. It is also possible to demonstrate in a substantial number of patients that CEA becomes significantly elevated

before metastatic disease can be detected by clinical or other diagnostic measures. This information can be best achieved by obtaining plasma samples for CEA assay preoperatively, 4 to 6 weeks postoperatively, and thereafter at regular intervals as an integral component of overall patient followup. While slowly rising levels may be more indicative of local recurrence, rapidly rising values reaching very high levels, usually in excess of 20 ng/ml, are found most often with hepatic and osseous metastases.

For patients with metastatic tumor, the CEA assay may complement standard clinical measurements of tumor response to therapy. However, as in the case of other clinical laboratory tests, there are examples of discordance between the observed change in tumor mass and the corresponding CEA values. In patients with advanced unmeasurable tumor, especially colorectal carcinoma, CEA assays may offer the only index to measure changes in tumor burden. Although definite criteria to aid in deciding whether to continue or alter therapy in patients with unmeasurable tumor, based on serial CEA determinations, are not established, it appears that a steadily, markedly rising titer is indicative of a poor therapeutic response. In such circumstances, each physician should make an individual decision whether CEA monitoring will be of clinical value in the management of a particular patient.

It is important to remember that raised values, due to various causes such as smoking, intercurrent infection, etc., can be seen in patients where the tumor is clinically stable and that decreasing CEA values are not invariably a sign of successful therapy. Furthermore, a proportion of patients with recurrent or advanced colorectal cancer may not show elevated plasma CEA values.

The role of CEA in the postoperative and therapeutic monitoring of patients with other types of cancer, such as pancreatic, gastric, and gynecological neoplasms, is less convincing than it is for colorectal cancer. In patients with metastatic breast cancer or lung cancer, especially small cell carcinoma, and significant CEA elevations, changes in CEA titers may be of value in reflecting response to chemotherapy. More studies are required to evaluate the role of CEA determinations for initiating or changing therapy in tumor types other than colorectal can-

cer.

The Panel would like to stress the view that the clinical utility of a tumor marker may be related to the efficacy of a therapeutic regimen. Where earlier recognition of disease progression is not accompanied by appropriate therapy, no benefit is gained. On the other hand, as more successful treatments for the major tumor types become available, CEA and other tumor markers will be more useful in the management of cancer.

Additional Needs

The Panel has identified several areas for future study which should improve the clinical utility of the CEA assay: The improvement of assay methodology; the evaluation of monoclonal antibodies to CEA for improving assay specificity; the establishment of a laboratory quality control system using a CEA standard preparation; the clinical study of CEA in combination with other markers; the diagnostic role of CEA in biological fluids other than plasma; the individual and collective comparison of CEA with other specific diagnostic modalities; the estimation of tumor CEA content in relation to plasma CEA values; and the study of the pathophysiology and metabolism of CEA.

This consensus Conference on CEA (Carcinoembryonic Antigen): its Role as a Marker in the Management of Cancer was sponsored by the National Cancer Institute, assisted by the Office for Medical Applications of Research, Office of the Director, NIH.

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LISTA DE ANUNCIANTES

ABBOTT LAB.
Tranxene Seminars

BOEHRINGER INGELHEIM
Alupent

BURROUGHS WELLCOME
Empirin w/Codeine

JANSSEN PHARM.
Vermox

Mc NEIL PHARM.
Haldol
Tylenol w/Codeine

ROCHE LAB.
Bactrim
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MINIPRESS[®] Effectively (prazosin HCl) by Reducing



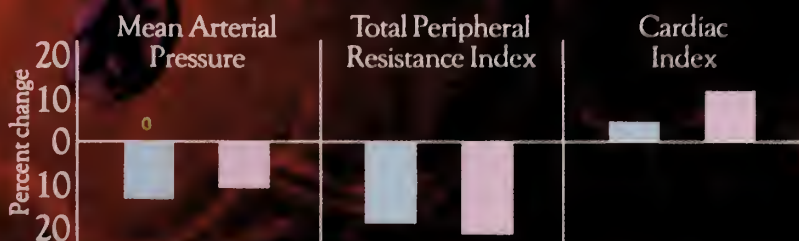
Artist's representation of the lumen of an arteriole, dilation of which results in reduced peripheral resistance and blood pressure.

Controls Hypertension Peripheral Resistance



- MINIPRESS Reduces Mean Arterial Pressure
- MINIPRESS Reduces Total Peripheral Resistance
- MINIPRESS Does Not Reduce Cardiac Index

...and Maintains These Effects Over the Long Term



Relative hemodynamic changes at rest and during exercise after one year of prazosin therapy in 10 hypertensive patients. Adapted from Lund-Johansen¹

■ Rest ■ Exercise

MINIPRESS[®]

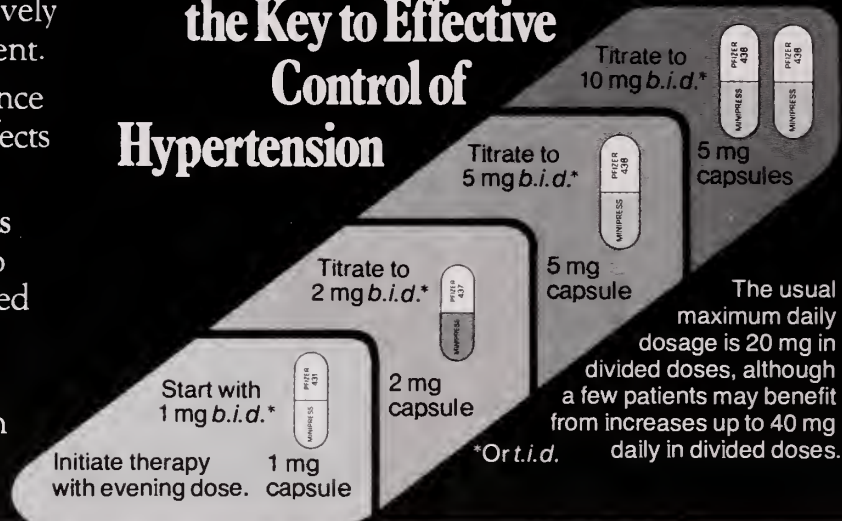
(prazosin HCl) Capsules 1 mg,
2 mg, 5 mg

MINIPRESS®

(prazosin HCl) Capsules 1 mg,
2 mg, 5 mg

- Effectively lowers elevated blood pressure by reducing peripheral resistance.
- Maintains cardiac output which allows patients to maintain an active life style.
- Maintains renal blood flow and glomerular filtration rate so it can be used effectively even in patients with renal impairment.
- Not a CNS agent so patients experience few of the troublesome CNS side effects that impair their quality of life.
- Cardiovascular response to exercise is preserved so patients are less likely to experience the fatigue often associated with beta-blocker therapy.
- A small percentage of patients have experienced orthostatic hypotension and syncope.

B.I.D. Dosage Titration... the Key to Effective Control of Hypertension



BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) CAPSULES For Oral Use

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and fundoscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

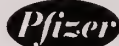
Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Reference:

1. Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in *Prazosin Clinical Symposium Proceedings*, published as a special report by *Postgrad Med.* New York, McGraw-Hill Book & Education Services Group, 1975, pp 45-52.



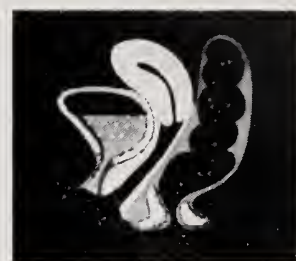
LABORATORIES DIVISION
PFIZER INC.

For recurrent attacks of urinary tract infection in women

Bactrim™ DS Double Strength Tablets

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Just one tablet b.i.d. for 10 to 14 days



- Action at urinary/vaginal/lower bowel sites helps eliminate reservoirs of infecting organisms
- Distinctive antibacterial action plus wide spectrum helps eradicate recurrent UTI
- Low incidence of bacterial resistance in community practice

- Convenient *b.i.d.* dosage provides day-and-night antibacterial control
- Contraindicated during pregnancy and the nursing period. During therapy, maintain adequate fluid intake; perform CBC's and urinalyses with microscopic examination.

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. Note: The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register*, 37:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. **Blood dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. **Allergic reactions:** Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. **Gastrointestinal reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. **CNS reactions:** Headache,

peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. **Miscellaneous reactions:** Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

Urinary Tract Infections: Usual adult dosage—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Recommended dosage for children—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

***Pneumocystis carinii* pneumonitis:** Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: Double Strength (DS) tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, Tel-E-Dose® packages of 100 Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. Oral suspension, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Please see back cover.

Her next attack of cystitis may require

the Bactrim™

3-system counterattack



ROCHE

Bactrim has shown high clinical effectiveness in recurrent cystitis as a result of its wide spectrum and distinctive antimicrobial action in the urinary, vaginal and lower intestinal tracts.

The probability of recurrent urinary tract infection appears to be enhanced by the establishment of large numbers of *E. coli* or other urinary pathogens on the vaginal introitus. The trimethoprim component of

Bactrim diffuses into vaginal fluid in effective concentrations, thus combating migration of pathogens into the urethra.

Studies have shown that Bactrim acts against *Enterobacteriaceae* in the bowel without the emergence of resistant organisms. Thus, Bactrim reduces the risk of introital colonization by fecal uropathogens. It has *no* significant effect on other normal, necessary intestinal flora.

Bactrim fights uropathogens in the urinary tract/vaginal tract/lower intestinal tract

Please see reverse side for summary of product information.

DISPLAY
SHELVES



BOLETIN

SOCIACION MEDICA DE PUERTORICO

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NUM. 4

ABRIL 1981

THE FRANCIS A. COWLEY
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10 SHAWNEE STREET
NEWTON, MASSACHUSETTS 02459

Feelings vs.

Some people feel that I am misused and overused and that I'm prescribed too often and for too many kinds of problems.

The FACT is that approximately eight million people, or about 5 percent of the U.S. adult population, will use me during the current year. By contrast, the national health examination survey (1971-1975) found that 25 percent of the U.S. adult population experiences moderate to severe psychological distress. Additionally, studies of patient attitudes revealed that most patients have realistic views regarding the limitations of tranquilizers and a strong conservatism about their use, as evidenced by a general tendency to decrease intake over time. Finally, a six-year, large-scale, carefully conducted national survey showed that the great majority of physicians appropriately prescribe tranquilizers.

Some people feel that patients being treated with anxiolytic drugs are "weak," can't tolerate the anxieties of normal daily living, and should be able to resolve their problems on their own without the help of medication.

The FACT is that while most people can withstand normal, everyday anxieties, some people experience excessive and persistent levels of anxiety due to personal or clinical problems. An extensive national survey concluded that Americans who do use tranquilizers have substantial

Facts

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON

AUG 13 1981

justification as evidenced by their high levels of anxiety. It was further noted that antianxiety drugs are not usually prescribed for trivial, transient emotional problems.

Some people feel afraid of me because of the stories they've heard about my being harmful and having the potential to produce physical dependence.

The FACT is that there are thousands of references in the medical literature documenting my efficacy and safety. Extensive and painstakingly thorough studies of toxicological data conclude that I am one of the safest types of psychotropic drugs available. Moreover, I do not cause physical dependence if the recommended dosage and therapeutic regimen are followed under careful physician supervision. However, I can produce dependence if patients do not follow their physicians' directions and take me for prolonged periods, at dosages that exceed the therapeutic range. Patients for whom I have been prescribed should be cautious about their use of alcohol because an additive effect may result.

Many of the most knowledgeable people feel that I became the No. 1 prescribed medication in America because no other tranquilizer has been proven more effective. Or safer.

The FACT is they are right.

For a brief summary of product information on Valium (diazepam/Roche) ®, please see the following page. Valium is available as 2-mg, 5-mg and 10-mg scored tablets.

Valium® diazepam/Roche

AVISO DE INTERES

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety, symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome; convulsive disorders (not for sole therapy). The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindications: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other anti-depressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. **Adults:** Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed, adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d., adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam/Roche) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10. Prescription Paks of 50, available in trays of 10.

La Junta Editora, consciente de su responsabilidad de hacer que el "Boletín" cumpla a cabalidad con su cometido de divulgar conocimientos médicos, elevar las normas de educación médica y al propio tiempo de llenar las necesidades de todos los compañeros médicos, ha acordado establecer una nueva Sección que se conocerá como "Sección de Preguntas".

Bajo esta nueva Sección, todos los compañeros tendrán la oportunidad de enviarnos preguntas médicas de casos difíciles o casos clínicos para opinión experta. Estas preguntas, con sus respuestas, serán publicadas en esta nueva Sección.

Las preguntas deberán ser enviadas a:

Boletín de la AMPR
Sección de Preguntas
Apartado 9387
Santurce, P. R. 00908

Esperamos sus preguntas.

Juan M. Aranda, MD
Presidente
Junta Editora



Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

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Fundado en 1903

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El Boletín se publica mensualmente. El precio de suscripción es de \$10.00 al año. Todo material de anuncio está sujeto a aprobación por la Junta Editora. La tarifa de precios para anuncios será suministrada a solicitud. Copia del anuncio debe ser recibida el día primero del mes que precede al mes de publicación. Representante de anuncios nacionales es la State Medical Journal Advt. Bureau, 711 South Blvd., Oak Park, Illinois 60302.

Podrán ordenarse reimpresos de los artículos a publicarse cuando se reciba notificación de su aceptación.

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El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica. El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista. La AMPR no se hace responsable de las opiniones y declaraciones vertidas por los autores y sus puntos de vista no necesariamente representan aquellos de la AMPR, cualquier relación con la política oficial es coincidencia.

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NEOSPORIN® Ointment (polymyxin B-bacitracin-neomycin)

Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs; in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

works just as well in their homes.

- It's effective therapy for abrasions, lacerations, open wounds, primary pyodermas, secondarily infected dermatoses.
- It provides broad-spectrum overlapping antibacterial effectiveness against common susceptible pathogens, including staph and strep.



- It helps prevent topical infections, and treats those that have already started.
- It contains three antibiotics that are rarely used systemically.
- It is convenient to recommend without a prescription.

NEOSPORIN® Ointment—for the office, for the home.
(polymyxin B-bacitracin-neomycin)

Effective • Economical • Convenient • Recommendable

Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs; in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section). Complete literature available on request from Professional Services Dept. PML.



Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

ASOCIACION MEDICA DE PUERTORICO

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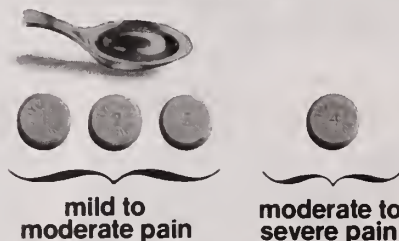


Lung cancer is now an equal opportunity tragedy.

Remember when lung cancer was a man's disease. Because men had been smoking longer than women. But the women's smoking boom that started in the 1930's and 40's—is paying most cruel dividends today. Yet most people still think lung cancer is a man's disease. Tell your female patients the true story. That lung cancer is now an equal opportunity tragedy. That's what "you've come a long way, baby" is all about.

TYLENOL[®] with Codeine

tablets @ / elixir @



Summary of Prescribing Information

Description

Tablets: Contain codeine phosphate*: No. 1—7.5 mg. (¼ gr.); No. 2—15 mg. (½ gr.); No. 3—30 mg. (½ gr.); No. 4—60 mg. (1 gr.)—plus acetaminophen 300 mg.

Elixir: Each 5 ml. contains 12 mg. codeine phosphate* plus 120 mg. acetaminophen (alcohol 7%)

***Warning:** May be habit forming

Actions: Acetaminophen is an analgesic and antipyretic; codeine an analgesic and antitussive.

Contraindications: Hypersensitivity to acetaminophen or codeine.

Warnings: *Drug dependence:* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to other oral narcotics. Subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Caution patients that codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with this drug may exhibit additive CNS depression. When such a combination is contemplated, reduce the dose of one or both agents.

Usage in pregnancy: Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Pediatric use: Safe dosage of this combination has not been established in children below the age of three.

Precautions: *Head injury and increased intracranial pressure:* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: Codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients: Administer with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: Most frequent, lightheadedness, dizziness, sedation, nausea and vomiting, more prominent in ambulatory than nonambulatory patients; some of these reactions may be alleviated if the patient lies down. Others, euphoria, dysphoria, constipation and pruritus.

Dosage and Administration: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. **TYLENOL with Codeine tablets** are given orally. The usual adult dose is: Tablets No. 1, No. 2, and No. 3: One or two tablets every four hours as required. Tablets No. 4: One tablet every four hours as required. **TYLENOL with Codeine elixir** is given orally. The usual doses are **Children (3 to 6 years):** 1 teaspoonful (5 ml.) 3 or 4 times daily, **(7 to 12 years):** 2 teaspoonful (10 ml.) 3 or 4 times daily, **(under 3 years):** safe dosage has not been established. **Adults:** 1 tablespoonful (15 ml.) every 4 hours as needed.

Drug Interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings. For information on symptoms/treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing.

TYLENOL with Codeine tablets are manufactured by McNeil Laboratories Co., Dorado, Puerto Rico 00646.

Caution: Federal law prohibits dispensing without prescription.

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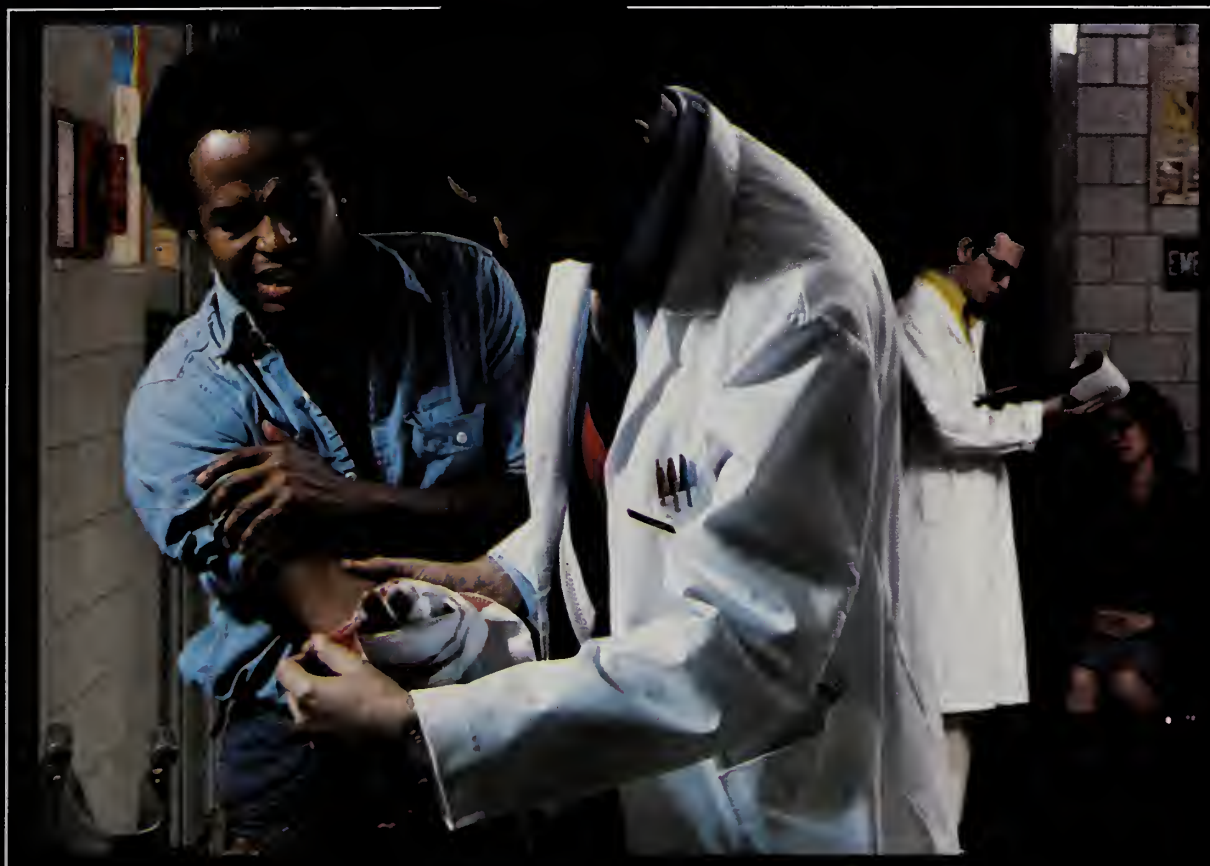
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McNEIL

McNeil Laboratories, McNEILAB, Inc.
Fort Washington, PA 19034

In the Emergency Department

Potent pain relief without aspirin complications



TYLENOL[®] with Codeine

tablets  / elixir 

Tablets Contain acetaminophen 300 mg plus codeine phosphate* as follows:
No.1—7.5 mg (1/8 gr); No.2—15 mg (1/4 gr); No.3—30 mg (1/2 gr); No.4—60 mg (1 gr)
Elixir Each 5 ml contains 12 mg codeine phosphate* plus 120 mg acetaminophen (Alcohol 7%)

*Warning: May be habit forming.

Please see facing page for summary of prescribing information

If you can't hold
the patient,
you can't hold
the pressure



Sculpture representing the
alpha central action* of Combipres®

Alpha...
hold the
pressure

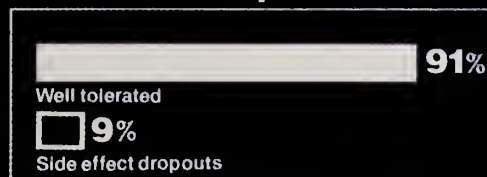
- central control of blood pressure*
- low incidence of impotence, depression, orthostatic hypotension**
- most common side effects are dry mouth, drowsiness and sedation, which generally tend to diminish with time. As with other agents containing diuretics, hypokalemia, hyperuricemia, and hyperglycemia may occur.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

**Orthostatic hypotension has been reported with chlorthalidone and may be potentiated when chlorthalidone is combined with alcohol, barbiturates, or narcotics.

plus...
hold the
patient

91% compliance[†]



[†]Of 484 patients in 16 clinical trials, only 9% definitely or probably dropped out due to side effects.¹

¹Data on file, Boehringer Ingelheim Ltd.

Please see brief summary on last page for warnings, precautions, and adverse reactions.

Combipres is not indicated for initial therapy. It is for patients responsive to its components given separately in equivalent dosages.

Combipres[®]

Each tablet contains: Catapres[®] (clonidine HCl)
0.1 or 0.2 mg, and chlorthalidone, 15 mg

.1 and .2

Hypertension

Alpha...plus

hold the pressure...
hold the patient...

Combipres® .1 and .2

Each tablet contains: Catapres® (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving

Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angio-neurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined

with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: Catapres (clonidine hydrochloride): Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.



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LA INMUNOLOGIA EN PUERTO RICO

Hace varios billones de años se hizo evidente que para que los seres unicelulares pudieran mutar ventajosamente, para que se pudiera identificar al organismo dañino o bizarro, habría que desarrollar un sistema de reconocimiento específico y sensitivo. Con una misión fundamental: discriminar lo propio de lo ajeno, protegiendo lo primero y destruyendo lo segundo, se formó el sistema inmunológico. Así, hecho con pericia y paciencia infinita, se constituye de moléculas libres y moléculas fijas en las membranas; de células circulantes y estacionarias, de corta y larga vida, de mucha y de poca actividad, pasivas y guerreras, grandes y chicas; en jerarquías, con mensajes para cerca y para lejos, instrucciones, órdenes; con armas destructoras; todo en ajetreo constante, hormigueando, husmeando, soltando anticuerpos acá y linfoquinas allá, acá una bacteria, allá una mutación, librando al ecosistema del truhán desconocido, de la célula enajenada, del invasor asesino. Y todo en armoniosa precisión, siguiendo un plan mayor y unas instrucciones escritas y detalladas, tallando en gestas guerreras cada uno de los movimientos y secuencias de lo que al fin es sólo el azar.

Hoy, muy pocos años en estudios, emerge este sistema tan vital, emerge su complejidad, y emerge el concepto de homeostasis inmunológica. Permea toda la biología y toda la medicina. Datos y más datos, detalles, asas cibernéticas, moléculas nuevas surgen de las páginas de libros y revistas cada día en mayor cuantía. El bordado no está completo pero ya se adivinan las siluetas que el futuro enhebrará en paisajes completos.

Aquí, en este volumen, se recoge parte del saber inmunológico del país. Algunos trabajos son resumen de presentaciones hechas durante el Primer Simposio de Inmunología llevado a cabo en la pasada Convención Anual de nuestra Asociación Médica. Hemos querido presentar un muestreo de las muchas áreas que abarca la inmunología contemporánea; de cuán envueltos están nuestros clínicos, de tan diversas especialidades, en practicar inmunología a diario; de la investigación inmunológica que se hace en el país; y un sumario de puntos prácticos aplicables a la medicina clínica. Es testimonio del avance de la disciplina mundial y localmente.

Eduardo A. Santiago Delpín, MD
María L. Santaella, MD

GUEST ARTICLE: THE VIEW FROM THE HEIGHTS OF IMMUNOLOGY

Sir Peter Medawar

Immunology is perhaps the most brightly lit domain of the medical sciences. The theoretical and therapeutic successes of this field and the generally hubristic air of its practitioners tend to arouse a certain amount of jealous resentment among, for example, pharmacologists and biochemists, who feel that their work is equally important and deserves to stand just as high in professional esteem. This is a small-minded view, for the success of immunology does nothing to diminish the importance of any other pursuit.

The therapeutic record of immunology is remarkable indeed. The discovery and definition of the blood groups long ago placed blood transfusion on a secure basis. Recognition of haemolytic disease (in which red blood cells are destroyed) of the newborn as an immunological misadventure led directly to a method of prevention that is applied very successfully in high-risk situations. The allergies and hypersensitivities, including the various forms of anaphylaxis (which results in shock and can sometimes be fatal), are also now known to be miscarriages of the immunological response - although the responses involved in allergies do not enjoy the relatively simple four-square character that distinguishes antibody formation against bacteria or viruses.

But in all such cases, the recognition of the antigen or immunity-provoking agent is a necessary precondition for prevention or cure. One of the most

surprising recent discoveries, made at the Medical Research Council's Clinical Research Center in London, is that the excrement of a house mite is an important element in the causation of asthma.

The rejection of grafts has been known for very many years to be an immunologic phenomenon, surprising though it may seem that one person's kidneys should be sufficiently unlike another's in chemical makeup to make rejection certain unless preventive measures are taken. These consist of annulling or otherwise modifying the character of the ordinary rejection process - a procedure which is now so successful that transplantation has been received into the ordinary repertory of surgical treatment.

But the very greatest triumph of immunology has been in the prevention of infectious disease. It is thanks to the scrupulous application of immunologic methods in the prevention of poliomyelitis and other diseases of viral origin that we can now say, with a huge sigh of relief, that poliomyelitis is on the way out, to be remembered - as smallpox will soon be remembered - only as one of the dangers that threatened mankind in the "bad old days."

The impending conquest of polio, to which the public health records of the United States and the countries of Northern Europe bear such eloquent testimony, does not seem to me to have received anything like the degree of professional recognition that it deserves. Until someone comes up with a safe and effective antiviral agent, prevention is likely to remain the safest bet for the management of all viral diseases.

Immunology has turned out to have enormous theoretic importance as well. Consider, for example, its impact on human genetics. The dis-

Sir Peter Medawar received the 1960 Nobel Prize for Physiology and Medicine for his work on Transplantation Immunology. This article is reprinted by permission from Sir Peter Medawar and The New York Times. ESD, MLS.

covery of the human blood groups made it possible to recognize a special pattern of polymorphism in human populations; that is to say, a stable differentiation of the human population into different genetic types identifiable by blood group membership. In just the same way, the discovery of tissue transplantation groups led to the recognition of an independent scheme of polymorphism in the human population. This, in turn, led to our first understanding of inborn differences in susceptibility to certain diseases, such as ankylosing spondylitis (a chronic, progressive form of arthritis), multiple sclerosis and the juvenile (insulin-dependent) form of diabetes. I suspect that it was these discoveries, as much as the relevance of tissue grouping to the transplantation of organs, that led the Nobel Committee to award the Nobel Prize for Physiology or Medicine in 1980 to George Snell, Jean Dausset and Baruj Benacerraf, the principals in the discovery of tissue transplantation groups. One of the puzzles about genetic polymorphism is how the subdivision of the population into distinct genetic types is maintained for generation after generation in spite of the mixing up process normally entailed by Mendelian inheritance; it is generally felt that some special selective force must be at work to keep this differentiation in being. In this connection, the recent discovery at the Sloan-Kettering Institute in New York, amplified by experiments at the Clinical Research Center in collaboration with Hendon Police College, disclosed the remarkable fact that a mouse's transplantation group had an important influence on its mating preferences. But how on earth can one mouse tell another's tissue group? The answer seems to be by smell, and this is where Hendon Police College's world famous system of training tracker dogs and their handlers came into the picture. It is not known if the cognate system of tissue groups in human beings affects their mating preferences, though it is of course common knowledge that smells influence sexual desirability, whether positively or negatively.

The Body as Its Own Enemy

As if we didn't have enough diseases already,

immunologic research has made it possible to recognize and classify a whole new category. These are the autoimmune diseases, in which the body reacts upon its own constituents as if they were foreign to it, i.e. as if they were non-self substances. Among such diseases are myasthenia gravis, characterized by faulty nerve conduction, lupus erythematosus, rheumatoid arthritis and in all probability, multiple sclerosis and one or two other neurological diseases. Washing of blood and cells and the administration of immunosuppressive drugs are among the methods used to combat these diseases.

During the past 10 years, hopes have been raised by the recognition of an immunologic element in resistance to tumors. Lewis Thomas, known to the public mainly as an author but to the profession as a wonderfully imaginative and inventive immunologist, propounded the theory that the rejection of organ grafts was a byproduct of the existence in the body of a monitoring system whose primary purpose was to spy out and eradicate all abnormal variants among tissue cells, especially cells that have undergone a malignant transformation. This is the theory of "immunologic surveillance." Theories of this stature are very seldom found to be straightforwardly right or wrong, but are to be valued by their power to stimulate and expedite research. In the examination of this theory much more has become known about the malignant transformation and about how to cope with cancer than would otherwise have been understood. On the other hand, the immunological defense against a tumor is nothing so simple as the process that leads to rejection of grafts. Work at the Sloan Kettering Institute has shown that experimental animals genetically or experimentally deprived of their ability to reject organ grafts are much more resistant to tumors than the theory of immunology surveillance would have tempted one to predict.

The practical outcome of immunologic investigations into cancer is the widespread adoption into clinical use of immunopotential — that is, procedures or agents that boost the immune response non-specifically. It is just possible that retinol (vitamin A) and some of its natural or synthetic derivatives belong to this category. Immunology has

also made possible the recognition of anaplasia as a common or perhaps universal characteristic of tumors, anaplasia being the formation anew in tumor cells of fetal or embryonic substances whose manufacture would normally have been switched off much earlier in life. So far no one has used this phenomenon therapeutically, but there is hope that it will aid in the early diagnosis of malignant states.

A Fascination with Specificity

Immunologic responses can be resolved into an interaction between an immunity-provoking agent and the antistubstance or antagonist for the formation of which it is responsible. This interaction is one of exquisite specificity. Indeed, immunologic methods are more sensitive and discriminating than any used in conventional chemistry or biochemistry. Some microbiologists, especially those interested in the treatment of infectious diseases, are rather impatient of the preoccupation of immunologists with specificity, since nonspecific defenses may be of paramount importance in resistance to

infection.

Recent discoveries tend to bear this out. Some blood cells - especially lymphocytes - transact specific immunologic responses, but other blood cells are now known to be "natural killer cells" which, when suitably activated, react upon a wide variety of non-self substances including, it would seem, cells that have undergone a malignant transformation or have been transformed by viruses. It may be that this is the direction in which the future application of immunology to cancer research lies.

The future of immunology as a medical science depends on the ever more radical analyses of the mechanisms of immune response that will eventually make it possible to bring the response under complete control, to be strengthened or weakened in one arm or another as the occasion calls for. There is every likelihood that immunology will bound forward in the future as it has in the past, if only because the practical importance of the problems it deals with, combined with the intellectual fascination of their analysis, will probably continue for many years to recruit into immunology some of the finest brains in medicine, surgery and the biological sciences.

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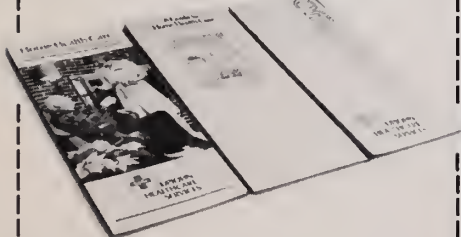
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COMPONENTES DEL SISTEMA INMUNE

María L. Santaella, MD

Podemos decir que la inmunología comenzó con el experimento de vacunación de Edward Jenner en el 1798, que se reconoció como una rama de la Medicina a fines del siglo 19, y que su desarrollo más reciente se le adjudica a la especialización de la inmunología en áreas tales como: la inmunoquímica, la inmunogenética y la inmunología celular.

Para conservar un concepto amplio de esta disciplina a pesar de su complejidad hoy, en el 1980, vamos a definir el Sistema Inmune como el Sistema de Defensa. Defensa en dos sentidos: 1) defensa contra lo extraño (característicamente los agentes infecciosos), y 2) defensa para preservar el ambiente interno cuando algunas de sus células han sido alteradas.

Este sistema de protección puede coordinarse en forma positiva para cumplir las funciones de defensa, o también puede dirigirse contra el mismo organismo como veremos a lo largo de las presentaciones subsiguientes.

El sistema-órgano responsable de la respuesta inmune es el sistema de los linfáticos, cuyas células están distribuidas por todo el cuerpo, pero concentradas en ciertos órganos: los nódulos linfáticos, el timo, la médula ósea y el bazo.

Los componentes del sistema inmune son los siguientes: Sistema Humoral, Inmunidad Celular, Componente Fagocítico y el Sistema de Complemento.

Para propósitos de simplificar, discutiremos a continuación el desarrollo del componente celu-

lar y luego el del componente humoral.

En el saco embrionario se identifica una célula precursora de las células linfoides que luego, alrededor de la semana cuarta a quinta, migra al hígado fetal.

De aquí divergen las dos subdivisiones fundamentales de los linfocitos que en su fase final representarán el componente celular por un lado, y el componente humoral por el otro.

Tomando la línea de inmunidad celular, sabemos que los precursores de células T pasan por un proceso de diferenciación, determinado en gran parte por información genética e independiente de estimulación antigénica. Para la semana sexta a octava se localizan en el timo, donde la influencia de factores solubles producidos por el timo será decisivo en su desarrollo. Alrededor de la semana número doce, circulan ya linfocitos T en la sangre periférica.

Por estimulación antigénica presentada a los linfocitos T por otro tipo de célula, el macrófago, o por estimulación antigénica directa, el linfocito T es activado, ésto es, preparado para ejercer sus funciones como célula efectora mediante la producción de mediadores.

Dentro del grupo de linfocitos T se reconocen varias subpoblaciones, algunas de ellas capaces de modular la respuesta de inmunidad celular y/o la respuesta de inmunidad humoral. Aquellas subpoblaciones que propician la respuesta inmune se denominan como linfocitos T colaboradores; aquellas que inhiben la respuesta inmune, como linfocitos T supresores. Además de su rol en cuanto a la respuesta inmune, se clasifican estas células a base de la presencia o ausencia de receptores y/o determinantes antigénicos.

Se reconoce un tercer tipo de linfocito T

TABLA I
Propiedades de las Inmunoglobulinas

	IgG	IgM	IgA	IgE	IgD
Concentración en suero mg por 100 ml.	1,200	100	280	0.025	3
Vida biológica, media en días	25	5	7	2.3	2.8
Fijación de complemento por la vía clásica	Sí	Sí	No	No	No
Transferencia plancetaria	Sí	No	No	No	No
Enlace con macrófagos	Sí	No	No	No	No
Actividad bactericida	+	+++	+	?	?
Actividad antiviral	+	+	+++	?	?

denominado como linfocito T con capacidad citotóxica, esto es, un linfocito activado con capacidad de destruir organismos o células, contra las cuales ha sido inducido a responder al recibir el estímulo apropiado.

Pasamos ahora a considerar la línea de desarrollo de la célula efectora de la inmunidad humoral.

Del hígado fetal surgen los precursores de linfocitos B que también experimentan un proceso de diferenciación a través del cual adquieren o pierden receptores y marcadores de superficie que los identifican. Se localizan en la médula ósea para la semana sexta a octava y circulan como linfocitos B para la semana número doce. Nuevamente por estimulación antigénica con o sin la coordinación de subpoblaciones de linfocitos T, el linfocito B se diferencia en célula plasmática, la cual producirá finalmente las inmunoglobulinas (producto final de la inmunidad humoral).

Tanto en el sistema T como en el sistema B hay un grupo de células que le confieren "memo-

ria" al sistema inmune. Estos linfocitos existen por un período mayor en comparación con los normales y son capaces de reconocer estímulos antigénicos previos y de iniciar una respuesta de inmunidad celular y/o humoral rápidamente al venir en contacto nuevamente con el estímulo antigénico.

La distribución de linfocitos T y B es variable en los diversos tejidos que forman parte del sistema-órgano inmune. En periferia, aproximadamente el 75 por ciento de los linfocitos son células T y el 25 por ciento B; en la médula ósea ocurre lo opuesto.

Volviendo al componente de inmunidad celular, la célula T tiene las siguientes funciones: 1) colaboración en la respuesta inmune, 2) supresión de la respuesta inmune, y 3) función de eliminación (erradicar bacterias ácido-resistentes, ciertas infecciones virales, infecciones por hongos y protozoarios).

En cuanto a los linfocitos B, representantes de la inmunidad humoral, identificamos la función principal de producir los distintos tipos de inmunoglobulinas. Las inmunoglobulinas a su vez: 1) protegen contra infecciones bacterianas, 2) neutra-

TABLA II
Funciones Biológicas del Complemento

Actividad	Componente(s) o fragmento(s)
Quimiotaxis	C3a, C5a, C567
Anafilotoxina *	C3a, C5a
Opsonificación	C3b
Citolítica	C5 a C9
Actividad parecida a quininas	Fragmento de C2
Neutralización de virus	C1 y C4
Mobilización de células desde la médula ósea a la periferia	C3e

* - Capacidad de causar una reacción parecida a la de anafilaxis debido a que produce contracción de la musculatura lisa, aumento de la permeabilidad vascular y liberación de la histamina de las células que la producen.

lizan virus, 3) actúan como barreras a lo largo del tracto gastrointestinal y respiratorio, 4) inician el proceso de destrucción de microorganismos por los macrófagos y ciertos tipos de linfocitos, y 5) causan la secreción de aminas vasoactivas producidas por las células cebadas y los basófilos.

Hay cinco tipos de inmunoglobulinas: IgG, IgM, IgA, IgD y la IgE y sus propiedades biológicas más importantes se ilustran en la Tabla I.

Hemos descrito brevemente dos de los cuatro componentes del sistema inmune, el sistema celular y el humoral.

Pasamos ahora al tercer componente: el Sistema Fagocítico, representado por dos tipos de células, los fagocitos circulantes que se denominan monocitos, y los fagocitos fijos, adscritos a los tejidos que se reconocen como los macrófagos.

Este sistema se desarrolla en la médula ósea, de los precursores llamados pro-monocitos. En san-

gre, circulan como monocitos y a nivel de los tejidos, se identifican como células especializadas para fagocitar: en el hígado, células de Kupffer; en el pulmón, macrófagos alveolares, etcétera. Los macrófagos pueden favorecer o inhibir respuestas de inmunidad celular y/o humoral.

El cuarto componente del sistema inmune es el Sistema de Complemento. Este sistema consiste de una serie de proteínas que se activan bajo ciertas condiciones en forma secuencial. Se han descrito dos vías: la clásica y la alterna.

Comenzando por la vía clásica, la misma puede activarse (ser iniciada) por IgG (subtipos 1, 2 y 3), IgM, y complejos inmunes (de antígeno y anticuerpo) entre otras cosas.

El enlace entre la inmunoglobulina y el primer componente de la vía clásica (C1) ocurre a través de una región específica en la molécula de inmunoglobulina, esto es, en una región del fragmento Fc

(el fragmento cristizable de la inmunoglobulina). Se activa C1 y actúa sobre la próxima proteína, C4. C4 se divide en dos fragmentos y C1 y C4 fragmentado actúan sobre C2, el cual a su vez se divide en dos fragmentos. C4 y C2 (en su forma fragmentada) forman una enzima capaz de dividir a C3 (la próxima proteína en la secuencia). De esta acción enzimática sobre C3 surgen dos fragmentos de gran importancia biológica: C3a y C3b, cuyas funciones detallaremos luego. Finalmente reaccionan los componentes terminales C5, C6, C7, C8 y C9 para llevar al resultado final de esta secuencia: daño a la membrana de la célula o del organismo (bacteria).

La vía alterna puede ser activada por: IgA, IgG, IgM y por IgE, o por sustancias producidas por bacterias, por materiales usados en estudios radiológicos o por las membranas usadas en ciertos equipos de diálisis entre otras cosas.

Una vez más, se activan proteínas en forma ordenada: el factor D actúa sobre el factor B y C3 para generar una enzima que divide a C3 en los mismos fragmentos que lo hace la enzima de la vía clásica. Continúa la activación de aquí en adelante de forma idéntica a la vía clásica. Properdina es una proteína que estabiliza la asociación entre el

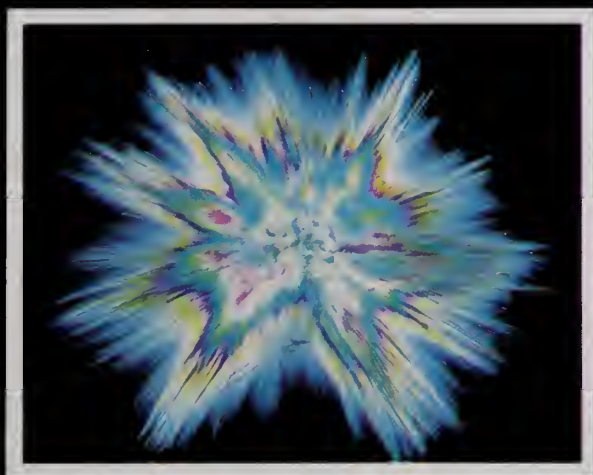
factor B y el fragmento C3b, generándose así más actividad de la vía alterna. El resultado de este proceso es daño a la membrana por inserción de estas proteínas, desequilibrio osmótico, producción de huecos y finalmente lisis.

Las funciones biológicas de los componentes de complemento y de los fragmentos que resultan a lo largo de la activación del sistema se incluyen en la Tabla II. Debe recalarse que desde el punto de vista de defensa, la función clave del complemento la tiene el fragmento C3b como molécula con la propiedad de opsonificación (proceso mediante el cual una bacteria o una célula es cubierta por un agente, como C3b, para hacer a la misma más susceptible a fagocitosis). Otra función importante de los fragmentos C3a, C5a y del complejo $\overline{\text{C567}}$ es la de quimiotaxis. Mediante este proceso, las células que van a participar en el proceso inflamatorio son dirigidas al área envuelta.

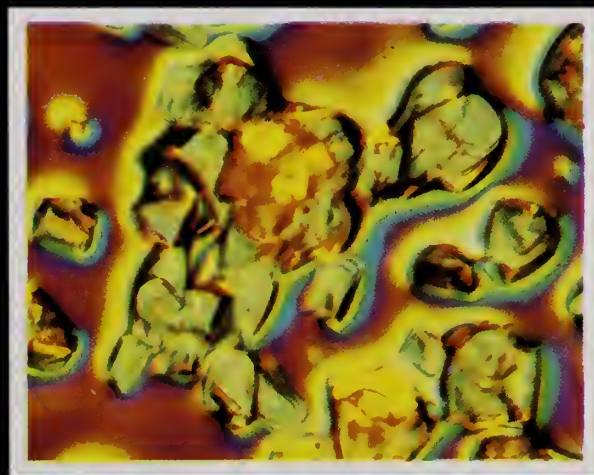
Para finalizar, deseo recalcar que la respuesta inmune no suele ser sencilla, esto es, no envuelve la intervención de un componente exclusivamente. Por el contrario, viene a representar la interrelación de los diversos participantes bajo regulación genética y/o la de una serie de mediadores.

THE BASICS

BEHIND A NEW
EFFECTIVE THERAPY FOR
HYPERTENSION



Prazosin crystal hydrated for purposes of photomicrographic illustration.



Polythiazide crystal hydrated for purposes of photomicrographic illustration.

INTRODUCING...

NEW

Minizide®



PRAZOSIN HCl/POLYTHIAZIDE

Capsules containing prazosin HCl equivalent to 1 mg, 2 mg or 5 mg prazosin plus 0.5 mg polythiazide

COMBINES TWO BASIC EFFECTIVE CONTROL



REDUCED
PERIPHERAL VASCULAR
RESISTANCE
WITH MINIPRESS®
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PRINCIPLES FOR THE OF HYPERTENSION

Prazosin and polythiazide crystals hydrated
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PLASMA VOLUME
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Capsules containing prazosin HCl equivalent to 1 mg, 2 mg or 5 mg prazosin plus 0.5 mg polythiazide



COMBINES TWO BASIC PRINCIPLES FOR THE EFFECTIVE CONTROL OF HYPERTENSION

BRIEF SUMMARY MINIZIDE® CAPSULES (prazosin hydrochloride/polythiazide) FOR ORAL ADMINISTRATION

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dose so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

INDICATIONS AND USAGE. MINIZIDE is indicated in the treatment of hypertension. (See box warning.)

CONTRAINDICATIONS. RENESE (polythiazide) is contraindicated in patients with anuria and in patients known to be sensitive to thiazides or to other sulfonamide derivatives.

WARNINGS. MINIPRESS (prazosin hydrochloride): MINIPRESS may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncope episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncope episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS. The incidence of syncope episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncope episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy.

RENESE (polythiazide): RENESE should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Thiazides may be additive or potentiative of the action of other antihypertensive drugs.

Potential occurs with ganglionic or peripheral adrenergic blocking drugs.

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medications such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop with thiazides as with any

potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate the metabolic effects of hypokalemia, especially with reference to myocardial activity.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in hepatic or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be either increased, decreased or unchanged. Latent diabetes mellitus may become manifest during thiazide administration.

Thiazide drugs may increase responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazides may decrease serum protein-bound iodine levels without signs of thyroid disturbance.

PRECAUTIONS. Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic or mutagenic studies have been conducted with MINIZIDE. However, no carcinogenic potential was demonstrated in 18 month studies in rats with either MINIPRESS or RENESE at dose levels more than 100 times the usual maximum human doses. MINIPRESS was not mutagenic in *in vivo* genetic toxicology studies.

MINIZIDE produced no impairment of fertility in male or female rats at 50 and 25 mg/kg/day of MINIPRESS and RENESE respectively. In chronic studies (one year or more) of MINIPRESS in rats and dogs, testicular changes consisting of atrophy and necrosis occurred at 25 mg/kg/day (60 times the usual maximum recommended human dose). No testicular changes were seen in rats or dogs at 10 mg/kg/day (24 times the usual maximum recommended human dose). In view of the testicular changes observed in animals, 105 patients on long term MINIPRESS therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on MINIPRESS alone for up to 51 months did not have changes in sperm morphology suggestive of drug effect.

Usage in Pregnancy: Pregnancy Category C. MINIZIDE was not teratogenic in either rats or rabbits when administered in oral doses more than 100 times the usual maximum human dose. Studies in rats indicated that the combination of RENESE (40 times the usual maximum recommended human dose) and MINIPRESS (8 times the usual maximum recommended human dose) caused a greater number of stillbirths, a more prolonged gestation, and a decreased survival of pups to weaning than that caused by MINIPRESS alone. There are no adequate and well-controlled studies in pregnant women. Therefore, MINIZIDE should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether MINIPRESS or RENESE are excreted in human milk. Thiazides appear in breast milk. Thus, if use of the drug is deemed essential the patient should stop nursing.

Pediatric Use: Safety and effectiveness in children has not been established.

ADVERSE REACTIONS. MINIPRESS (prazosin hydrochloride): The most common reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS, some of them rarely (in some instances exact causal relationships have not been established):

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular: edema, dyspnea, syncope, tachycardia.
Central Nervous System: nervousness, vertigo, depression, paresthesia.
Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

RENESE (polythiazide): Gastrointestinal: anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.

Central Nervous System: dizziness, vertigo, paresthesia, headache, xanthopsia.
Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.
Dermatologic: purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis).
Cardiovascular: orthostatic hypotension may occur and be aggravated by alcohol, barbiturates or narcotics.
Other: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness.

OVERDOSAGE. MINIPRESS (prazosin hydrochloride): Accidental ingestion of at least 50 mg of MINIPRESS in a two year old child resulted in profound drowsiness and depressed reflexes. No decrease in blood pressure was noted. Recovery was uneventful.

Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate that MINIPRESS is not dialyzable because it is protein bound.

RENESE (polythiazide): Should overdosage with RENESE occur, electrolyte balance and adequate hydration should be maintained. Gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium and other electrolyte therapy, administered with caution as indicated by laboratory testing at appropriate intervals.

DOSAGE AND ADMINISTRATION. MINIZIDE (prazosin hydrochloride/polythiazide): Dosage, as determined by individual titration of MINIPRESS (prazosin hydrochloride) and RENESE (polythiazide). (See box warning.)

Usual MINIZIDE dosage is one capsule two or three times daily, the strength depending upon individual requirement following titration.

The following is a general guide to the administration of the individual components of MINIZIDE.

MINIPRESS (prazosin hydrochloride): Initial Dose: 1 mg two or three times a day. (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

RENESE (polythiazide): The usual dose of RENESE for antihypertensive therapy is 2 to 4 mg daily.

HOW SUPPLIED.

STRENGTH	COMPONENTS	COLOR	CAPSULE CODE	PKG SIZE
MINIZIDE 1	1 mg prazosin + 0.5 mg polythiazide	Blue-Green	430	100's
MINIZIDE 2	2 mg prazosin + 0.5 mg polythiazide	Blue-Green/Pink	432	100's
MINIZIDE 5	5 mg prazosin + 0.5 mg polythiazide	Blue-Green/Blue	436	100's



LABORATORIES DIVISION
PFIZER INC.

ESTADOS DE DISINMUNIDAD

E.A. Santiago Delpín, MD

Al igual que el sistema cardiovascular, gastrointestinal y endocrino viven en perenne y delicado balance homeostático, así el sistema inmune parece tener numerosas asas cibernéticas las cuales definen la respuesta inmunológica. Es un sistema muy complicado; quizás más que otros. Y cada día se descubre más variedad morfológica y funcional, y más interacciones entre los distintos componentes. Conviene que hoy comencemos a conceptualizar una "homeostasis inmunológica", ya que este paso facilitaría la comprensión y unificación de fenómenos patológicos definidos, y la influencia del ambiente en la función inmune. La Figura 1 ilustra mi interpretación del sistema inmune.

Siendo un sistema multicelular variado está sujeto a influencias congénitas y a influencias del ambiente. Llamaremos un "estado de disinmunidad" a las disfunciones que ocurran como resultado de influencias nocivas extraordinarias y que se manifiesten como enfermedad específica, como aumento en susceptibilidad a enfermedad, o como alteración en las pruebas de función inmunológica celular o humoral. Nos parece clasificarlas en CONGENITAS y ADQUIRIDAS, sub-dividiendo estas últimas en NATURALES y ARTIFICIALES.

Desde que Brutton describió un caso de agamaglobulinemia en 1953, se han descrito decenas de condiciones CONGENITAS con daño al sistema inmune. La etiología no es conocida aunque algunas son transmitidas genéticamente y se sospecha base hereditaria en ellas. Un arresto en la maduración a distintos niveles explica la variedad en los tipos de de-

fecto, y un postulado sistema multialélico explica la variedad en la severidad de los defectos (Tabla I). La mayoría de las enfermedades congénitas son sintomáticas; la mayoría son severas; y algunas son incompatibles con la vida. La disfunción específica depende de la línea celular lesionada, pero en casi todas hay susceptibilidad aumentada a infecciones. La muerte suele ser séptica.

La DISINMUNIDAD ADQUIRIDA es aquella con que nos confrontamos después de nacido y que probablemente no está sujeta a tanto control genético con excepción de los cambios que ocurren en la madurez del sistema inmunológico. Discutiremos primero las condiciones de DISINMUNIDAD NATURAL. El recién nacido y el envejeciente ambos tienen un sistema inmunológico ineficiente (1, 2). El primero porque todavía no ha madurado su sistema: se especula si esta inmadurez es un rasgo genéticamente controlado o si es simplemente que no ha venido en contacto con un número suficiente de antígenos para desarrollarse en pleno. En el envejeciente se ha correlacionado con la edad una disminución severa en la respuesta inmunológica, sobre todo después de los 60 años, que consiste inicialmente en una involución del timo, una disminución y eventualmente desaparición de la timosina y una disminución en las funciones mediadas por células T incluyendo ambas T ayudantes y T supresoras. Eventualmente las respuestas están ausentes o, por lo menos, bizarras incluyendo el desarrollo de auto-anticuerpos, y de complejos inmune (3). Esto ocurre en el hombre y en algunos roedores.

Otras condiciones se enumeran en la Tabla II, incluyendo la hiporeactividad inmunológica que ocurre en estados de enfermedades auto-inmunes. Así mismo los estados de cáncer avanzado y las infecciones con organismos crónicos conllevan una disminución en la función inmunológica haciendo-

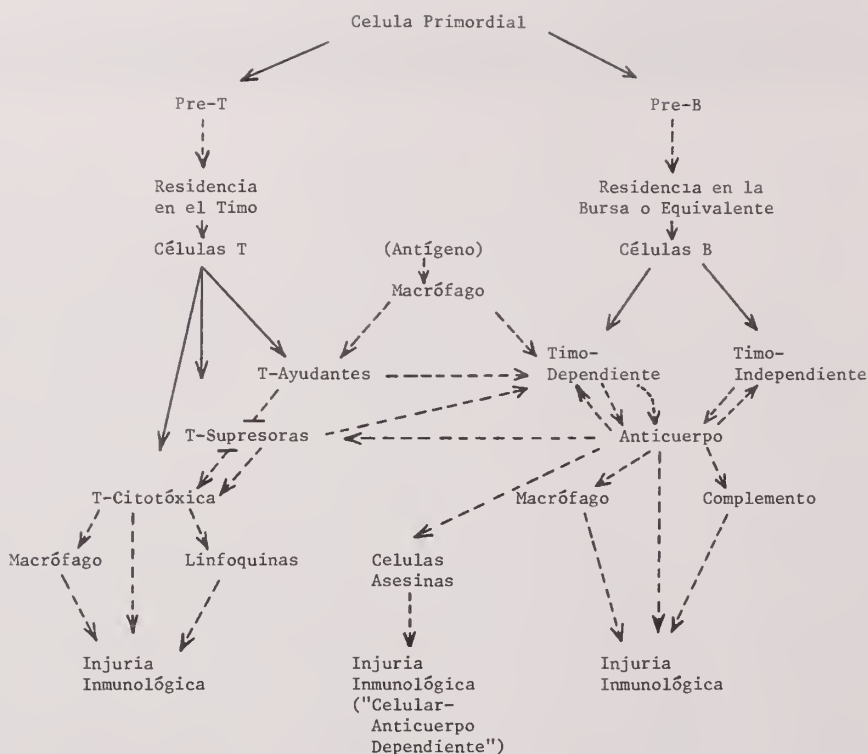


Fig. I.: Interacción de los Componentes del Sistema Inmunológico (——— Origen A:)
(- - - - - Influencia sobre o Producción de:)

nos más susceptibles a todavía más infecciones o tumores. La sepsis aguda conlleva una depresión del sistema inmune muy severa al igual que la conllevan los virus (4). El diabético tiene su inmunidad disminuída y recientemente se ha descrito la presencia de complejos inmunes circulantes (3). Aunque la relación con la patogénesis de la diabetes no está clara, sí lo está, y se ha conocido por siglos la susceptibilidad del diabético a infecciones, susceptibilidad que hoy atribuimos a déficit inmunológico (5). Esto ha sido comprobado en ratones (6, 7). Al igual, la tecnología moderna nos ha permitido detectar también en el urémico un estado de hiporeactividad inmunológica. El lugar de residencia de la dis inmunidad urémica no está claro aunque se piensa que hay factores supresores circulantes que afectan la función de los linfocitos T (8). El embarazo ha sido

motivo de estudios extensos en los últimos quince años identificando que hay una disminución de la inmunidad celular y humoral específica, pero también con algunos efectos generales. Aunque la relevancia en el embarazo humano no es clara, en ratones la dis inmunidad del embarazo aparenta causar susceptibilidad a infecciones (9).

La relación de la nutrición con las defensas del cuerpo ha sido conocida por siglos y motivo de estudios intensos en los últimos veinte años. Uno de los estudios más dramáticos y trágicos que conocemos se llevó a cabo por médicos judíos en el getto de Varsovia ilustrando el efecto de la mala nutrición en el organismo y en particular en el sistema inmunológico (10). Subsiguientemente, la mala nutrición aguda o crónica se ha mostrado afectar el sistema inmune, en ambas serie celular y serie hu-

TABLA I

Disinmunidad Congenita

A.	En el Sistema — T	(8 síndromes)
B.	En el Sistema — B	(7 síndromes)
C.	Combinados	(4 síndromes muy severos)
D.	En complemento	(Todos sus componentes)
E.	En la fagocitosis	(18 síndromes)

TABLA II

Disinmunidad Natural

A.	El joven y el envejeciente
B.	Infección crónica
C.	Sepsis
D.	Viruses
E.	Cáncer avanzado
F.	Autoinmunidad
G.	Diabetes melitus
H.	Uremia
I.	Dietas altas en grasas
J.	(Obesidad??)
K.	Malnutrición aguda y crónica
L.	Embarazo

moral (11). La función fagocitaria se lastima también (11). Sorprendentemente, estudios llevados a cabo en varios laboratorios incluyendo los nuestros en Puerto Rico, demuestran lo inverso, que las dietas altas en grasas alteran la respuesta inmune de manera que la respuesta a retos celulares está disminuída. Experimentos llevados a cabo en nuestros laboratorios indican que disminuye el rechazo inmunológico alogénico de piel y tumores en ratones (12), disminuye la transformación blástica de linfocitos a PHA y disminuye la producción de factor de inhibición (13), disminuye la capacidad de linfocitos humanos y murinos de formar grumos polares (14), disminuye la reactividad dermal a DNCB en ratas (15),

y disminuye la producción de anticuerpos en contra de albúmina bovina y lisocima en ratones (16). Estos hallazgos sugieren cautela en las recomendaciones de los requisitos grasos de la dieta.

La DISINMUNIDAD ARTIFICIAL O AC-CIDENTAL, prenda y regalo del hombre para el hombre y resultado de nuestros "avances" tecnológicos y sociales, la veremos cada día más en la práctica de nuestra medicina. Ejemplos específicos incluyen el estado de disinmunidad que ocurre con la esplenectomía y con la timectomía. La timectomía, aún en adultos, produce una disminución en las funciones mediadas por células T. La esplenectomía tiene el efecto de disminuir la resistencia a organismos

extra-celulares encapsulados. Además, la esplenectomía tiene efectos adicionales sobre una gran cantidad de pruebas celulares, resistencia a tumores, parásitos, etc., ya que la población residente del bazo es sumamente compleja y heterogénea. Se discute este tema en el trabajo de Roselló, en este volumen. Estados de trauma múltiples, de shock, y las quemaduras han sido todos asociados con una disminución muy profunda de la inmunidad celular y humoral (17-19). Usando una gama de pruebas sofisticadas se ha identificado que las respuestas de las células T al igual que a células B, están muy disminuidas. Indudablemente es éste un factor de tremenda importancia en la susceptibilidad tan grande a infecciones que vemos en este tipo de paciente. No solo en estados de injurias extremas sino en la cirugía general que llevamos a cabo todos los días, y aun en la anestesia nada más, se ha demostrado también una disminución muy profunda, aunque transitoria, de la respuesta celular (20, 21). Estas observaciones se llevaron a cabo durante la última década y han hecho al cirujano mucho más consciente del poco margen que se tiene aun en personas normales que se someten a anestesia y cirugía.

Algunos antibióticos, en especial algunas tetraciclinas son responsables de producir una disminución en la síntesis de DNA en linfocitos estimulados (22). El alcoholismo agudo también conlleva un estado de dis inmunidad más o menos severo pero reversible al llegar a la sobriedad (23). Otros estados de tensión neural también causan dis inmunidad (24). Los estados de inmunosupresión clínica, obviamente, llevan como función el producir un estado de dis inmunidad, pero de lo que no se está consciente es de cuántas son las drogas que nosotros usamos que conllevan estos riesgos, y con cuánta frecuencia se están usando. Por ejemplo se usan inmunosupresores en trasplante, en quimioterapia del cáncer, en enfermedades reumáticas, enfermedades de la piel, oculopatías, alergias, infecciones, etc., de manera que aunque no las llamemos "inmunosupresoras", están estos pacientes literalmente inmunosuprimidos. Finalmente, la hemodiálisis *per se* y otros circuitos extra-corpóreos, y el oxígeno hiperbárico se han asociado con un estado de dis inmunidad.

Este breve listado nos lleva a la conclusión inexorable que los estados de dis inmunidad son más

frecuentes de lo que sospechábamos. Y así como la homeostasis renal, la cardiovascular y la gastrointestinal se desbalancean con tanta facilidad, ante tanto agente externo, así mismo la homeostasis inmunológica es también sujeta a desbalance frecuente y severo. Creemos que es nuestra responsabilidad el estar más consciente del concepto de homeostasis inmunológica, y de que probablemente nos veamos en la obligación de comenzar un estudio más concienzudo del estado inmunológico de los pacientes que tenemos.

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SOME USES AND LIMITATIONS OF IMMUNOLOGIC TESTING IN HUMAN PATIENTS

Julio A. Lavergne, PhD

What is immunologic competence? Although there is not a simple answer to this question, we generally agree that we are immunocompetent when our body defense forces are able to recognize and neutralize any agent which could disturb our internal metabolic environment. Such defense is provided by the two (T and B) arms of the immune system, which participate in the augmentation of the more basic, nonspecific protective mechanism of phagocytosis. Although we distinguish important functions for the T-lymphocyte system (cellular immunity) the B-lymphocyte system (humoral immunity) and the phagocytic system, relatively little is known about the nature of the cells involved, their interrelationships or their functional products. Immunologic testing is presently being used in conjunction with other laboratory procedures in the diagnosis and prognosis of disease states, and in the assessment of immunologic function. There are numerous *in vivo* and *in vitro* tests which may be used in the evaluation of specific or nonspecific immunologic function in patients suffering from infectious, autoimmune, immunodeficient or neoplastic diseases. These tests have been classified (1) in three categories which are:

1. Test for Nonspecific (primary) immune responses.
2. Tests for Specific (secondary) immune responses.

3. Test for tissue-damaging (tertiary) immune responses.

Tests which fall within the first category are those which evaluate the inflammatory response and the phagocytic function of the patient. Tests for secondary immune responses include those which quantify B and T subpopulations of lymphocytes, and measure humoral (antibody) and cellular (delayed hypersensitivity) function. Tertiary immune responses are evaluated by tests of reagin (IgE) hypersensitivity, tests of cytotoxic and immune complex injury, and tests of injury due to delayed hypersensitivity. The present discussion is limited to some of the presently available tests which have applications in the detection of anti-tumor immune responses.

The assessment of the immune response to neoplastic diseases in humans has increasingly become more valuable in the proper diagnosis, prognosis and monitoring of anti-tumor therapy. Reducing the high rate of mortality in neoplastic diseases depends on their early detection, thorough treatment, and appropriate management and follow up (2). While considerable progress has been made in the development of methods for early detection and management in several diseases such as Burkitt's lymphoma, malignant melanoma and sarcomas, by the use of immunofluorescence and immunoprecipitation techniques (Burkitt's lymphoma), immunofluorescence and cytotoxic antibody tests (melanocarcinoma), and immunofluorescence techniques (sarcomas) (3), it is still necessary to rely on less than adequate clinical impressions for initial diagnosis, management and follow-up of most neoplastic diseases (4). Recently, considerable progress towards the development

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of sensitive and reliable diagnostic and prognostic tools has been made using immunological methods (5).

The immune response of human tumor hosts to tumor associated antigens (TAA) has been clearly demonstrated (6, 7, 8, 9, 10). The presence of this anti-tumor response is believed to influence tumor development, growth and metastasis (6). Many attempts have been made to correlate the overall immunological status of cancer patients with prognostic aspects of the disease (11, 12). Skin test results are currently regarded as the most useful *in vivo* correlates of cell-mediated immune status in tumor patients (11, 12, 13, 14). Skin testing with common sensitizing antigens (DNCB, KLH) (15, 16, 17, 18) and with ubiquitous recall antigens (Candida, Trichophyton, SKSD, PPD) (16, 17) has been useful for the determination of the afferent and effluent immunological status of the patient, indicating the patient's competence in becoming sensitized and later responding to the pertinent stimulating antigen. Detection of specific anti-tumor immune responses also has been done by assessing skin test reactivity to antigenic extracts of autologous or allogeneic tumors (12, 13, 14). Even though the observation of positive skin test reactions to TAA extracts shows that the patient is capable of mounting an anti-tumor response, no correlation has been clearly defined between these results and prognostic aspects of the disease (14). Limitations of the skin test include a low degree of sensitivity (18), difficulty in the interpretation of results because of the subjectivity involved in reading them, and the lack of correlation with clinical status of the disease because of the long period of reactivity after initial antigenic stimulation (18). Several different *in vitro* methods using human peripheral blood leukocytes (PBL) for the measurement of cell-mediated immune responses to a variety of antigens are currently being studied (6). Some of these methods (target cell cytotoxicity, detection of migration inhibitory factors, etc.) surpass skin testing in reliability and offer a wider range of possibilities concerning the sequential responsiveness of the subject under study. Methods measuring target cell destruction or growth inhibition reflect on the ability of immune

lymphocytes to interact with specific target cells. However, the specificity of these reactions is questionable and the techniques are elaborate (18). Methods involving antigenic stimulation of lymphocytes and their resulting transformation into blast forms have similar limitations as *in vitro* tools for the assessment of cell-mediated immune reactions (18). Blastogenesis assays detect only the afferent branch of the immune response, possibly indicating only the primary recognition of antigenic differences, without giving evidence of effector functions of the immune cell.

Migration inhibition assays are other *in vitro* assays of cell-mediated immunity in the human (19, 20). Results of these tests seem to correlate well with skin test results using several antigens including tumor cell extracts (18). The method is sensitive to small quantities of antigen and has shown a promising degree of correlation with clinical parameters in some human tumors, such as breast, lung, and colon carcinomas and malignant melanoma (21, 22, 23, 24, 25). Moreover, it also exhibits a high degree of antigenic specificity (18). The migration inhibition method offers a distinct advantage over skin tests in being considerably less subjective in its interpretation. Moreover, among tumor patients migration inhibition reactivity has been shown to fluctuate in time, reflecting changes in the clinical status of the host. This observation offers the possibility of monitoring the progress of the patient undergoing therapeutic treatment.

Given the potential advantages of the migration inhibition assay method over other approaches to the assessment of tumor immunity, we explored its usefulness in a model of human transitional cell carcinoma of the urinary bladder. In these studies we investigated the *in vitro* migration response of peripheral blood leukocytes (PBL) from bladder transitional cell carcinoma (TCC) patients, patients with other genitourinary diseases, and normal control individuals to bladder tumor antigens, using a leukocyte migration inhibition (LMI) method (26). Antigens used were derived from allogeneic bladder tumor cell lines by hypertonic potassium chloride extraction (27). Since the LMI response is mediated by leukocyte inhibitory factor (LIF), a lym-

TABLE I

LMI Response* of Bladder Carcinoma Patients, Patients with Other Genitourinary Disease, and Normal Control Individuals

	Patients with Bladder Carcinoma	Patients with other Genitourinary Diseases	Normal Control
Number of Positive LMI tests	61	6	0
Number of Negative LMI tests	63	18	26
Total number of subjects tested	124	24	26

* - All subjects' lymphocytes were tested with an antigen preparation derived by potassium chloride (KCl) extraction from the human bladder carcinoma cell lines RT4 or T24.

phokine elaborated by antigen-stimulated sensitized lymphocytes (28), this assay provides an *in vitro* correlate of host cell-mediated immunity to tumor-derived antigens. Results obtained suggest that this *in vitro* assay method may prove valuable in monitoring bladder tumor patients for completeness of initial tumor resection and for clinical recurrence, as well as for further studies of the tumor-specific immune response in this disease.

Table I shows results which demonstrate *in vitro* migration inhibition of leukocytes from patients with transitional cell carcinoma of the bladder in response to KCl extracts of epithelial cell lines derived from such tumors. The occurrence of positive results in some patients with other genitourinary diseases and the presence of a substantial subpopulation of bladder tumor patients with negative assays indicate that this method as performed here is not useful as a diagnostic tool for human transitional cell carcinoma. However, bladder tumor patients were shown to consist of LMI positive and negative subpopulations which proved to be correlated with the presence or absence of tumor at the ti-

me of assay (Table II). These results imply a direct relationship between the presence of viable tumor cells in the host and circulating tumor-reactive lymphocytes.

An *in vitro* method such as the one employed in this study may have a number of uses in the management of cancer. The greatest usefulness of an assay in the diagnosis of cancer would reside in its ability to discriminate well between the normal state, various benign diseases, and cancer. An assay that can make this distinction in early stages of the disease would be of particular value. However, LMI results observed with TCC patients indicate that the LMI method does not fulfill all the requisites essential for its diagnostic applicability. While it is able to detect the presence of tumor in the patient in most cases, and to discriminate the tumor state from the normal state (no TCC disease), some non-discrimination is apparent between bladder TCC, chronic cystitis and carcinoma of the renal pelvis.

For therapeutic application, an assay should demonstrate that anergy in the patient is not the usual state, by showing the presence of immune reactivi-

TABLE II
Correlation between LMI response* and presence of tumor at the time of assay

	Bladder carcinoma patients with tumor present	Bladder carcinoma patients with tumor absent
Number of positive LMI tests	17**	5
Number of Negative LMI tests	3	18**
Total Number of Patients Tested	20	23

* - The antigen used for the LMI test was derived from the human bladder carcinoma cell line RT4.

** $p < 0.001$ by Chi Square analysis.

ty against tumor antigens at some stage of the disease. The present results have shown that this is the case with LMI response of PBL from TCC patients, which are detectable in those patients harboring tumor at the time of assay, but not after tumor resection.

Furthermore, an assay may not need to provide absolute diagnostic specificity in order to have prognostic value. However, its results would need to correlate with clinical status, regardless of the mechanism involved. Results of LMI assays performed with TCC patients' PBL show that a strong correlation exists between positive assay results and presence of tumor in the host at the time of assay, indicating the potential prognostic value of this method in transitional cell carcinoma of the urinary bladder.

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INMUNOSUPRESION CLINICA

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La inmunosupresión es utilizada cada vez más en diversas condiciones clínicas tales como enfermedades colágenas, autoinmunes, alérgicas, cáncer, y más extensamente en trasplante de órganos y tejidos. Existen diferentes métodos de inmunosupresión. Algunas modalidades incluyen la destrucción de las células inmunocompetentes antes del trasplante; la conversión del antígeno en formas que no se reconozcan; inhibición de la transformación y proliferación del linfocito; la destrucción inhibitoria de las células del injerto por los linfocitos "matadores", limitando la diferenciación de los linfocitos; activando las células supresoras; y finalmente, previniendo el daño tisular producido por las células no específicas o aquellas activadas por el complejo antígeno-anticuerpo o por células sensibilizadas.

Aunque existe investigación activa en todas estas áreas, no todas son de utilidad clínica. Contamos actualmente con un pequeño grupo de agentes inmunosupresores, que constituyen las principales armas clínicas. Los podemos clasificar según su acción, como sigue:

I. Agentes Antiproliferativos

- A. antimetabolitos
- B. agentes alquilantes
- C. antibióticos tóxicos
- D. rayos X

II. Agentes que producen privación de linfocitos

- A. suero antilinfocítico
- B. esteroides adrenales
- C. timectomía
- D. drenaje del ducto torácico
- E. rayos X

Los agentes antiproliferativos (mutágenos químicos) producen alteraciones químicas y/o físicas en el DNA, RNA, o en la síntesis de proteínas. El daño producido al DNA puede tomar diferentes cursos (Fig. 1). Puede haber reparación con síntesis normal, produciendo células normales. Puede no haber reparación, con resultante muerte celular. Por último, puede haber reparación parcial o anormal, produciendo un error en la síntesis de reparación que a su vez produzca un daño focal (selectivo a una línea de células), o produciendo líneas de células anormales. En el primer caso se produce un efecto antiviral, anti-cáncer e inmunosupresor. En el segundo se producen errores en la germinación, mutaciones o cáncer. El rumbo a tomar va a depender del tipo de célula y el estadio en que se encuentre; de la dosis, ruta de administración de la droga, tiempo en que se use el agente, factores genéticos, condición del huésped, agentes adyuvantes y promotores que se utilicen. Las cualidades de un agente inmunosupresor ideal serían: (1) especificidad, y (2) poca o ninguna toxicidad. Sin embargo, los agentes inmunosupresores con que disponemos están lejos de ser ideales por lo que debemos mantener presente sus complicaciones al utilizarlos.

Entre los agentes antiproliferativos más comunes, el linuran (azatioprina) es el más usado. Este es un antimetabolito análogo de las purinas. Su

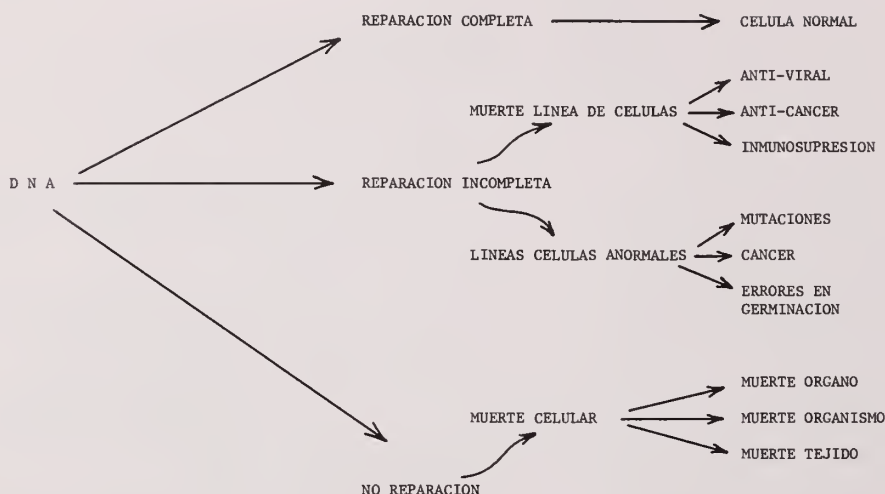
EFFECTO DE AGENTES INMUNOSUPRESORES SOBRE LA MOLECULA DE DNA

Figura 1: Efecto de agentes inmunosupresores sobre la molécula de DNA.

estructura es similar a la 6-mercaptopurina con un anillo imidazol conectado al grupo sulfhidrido del carbono o que le da mejor estabilidad a la molécula al evitar su rápida metilación y oxidación. Es activo principalmente en células en replicación rápida, como lo son los linfocitos T. En la mayoría de los centros de trasplante la utilizan como parte de la inmunosupresión profiláctica en las dosis ilustradas en la Tabla I.

Los efectos tóxicos del Imuran son principalmente en la médula ósea produciendo leucopenia, anemia, y trombocitopenia. Por tanto, las dosis se deben ajustar a los niveles de plaquetas y glóbulos blancos. Drogas como el "allopurinol" potencian la acción de la azatioprina requiriendo especial precaución al usarla. Otra complicación importante es el daño hepático (colestasis intrahéptica) que usualmente es mínimo, pero podría progresar a niveles letales para el paciente. Se manifiesta con elevación de leve a moderada de la bilirrubina y las enzimas hepáticas. El diagnóstico se confirma por medio de biopsia de hígado. Si se confirma se debe sustituir la droga por ciclofosfamida que es menos hepatotóxica. Aun en casos de dis-

función hepática infecciosa, ayuda a veces el sustituir la azatioprina. Otras complicaciones incluyen fiebre, lesiones de piel, síntomas gastrointestinales, miopatías, pancreatitis y otras menos específicas.

Dentro de los agentes aquilantes uno de los más usados es el Citoxan (ciclofosfamida). Este posee un anillo altamente reactivo como parte de su molécula. En este anillo hay muchos lugares de fácil combinación con los nitrógenos terciarios de las purinas y pirimidinas o con los grupos carboxilos, sulfhidrilos, amino y fosfóricos de muchas moléculas (DNA; RNA; enzimas; y proteínas). Starzl demostró la utilidad de la ciclofosfamida en trasplante de hígado y riñón como agente primario. La dosis es la mitad de la azatioprina. Aunque actúa en diferente fase del ciclo celular tiene efectos secundarios similares por lo que debe seguirse con conteo de células blancas y plaquetas de cerca. Complicaciones de la ciclofosfamida incluyen: estomatitis, náuseas, vómitos, diarreas, reacciones de piel, alopecia, anemia, cistitis hemorrágica, y toxicidad cardíaca.

Dentro del grupo que produce privación de linfocitos se encuentran los esteroides. En éstos

TABLA I

Uso Profiláctico del Imuran

Prequirúrgico	5mgs/kg/d oral por dos días
1er y 2do día	5mgs/kg/d
3er a 6to día	4mgs/kg/d
Séptimo día en adelante	3mgs/kg/d
Mantenimiento	2.5mgs/kg/d

no solo se aprovecha la acción no específica anti-inflamatoria, sino, que también penetran la membrana celular y se combinan con receptores específicos intracelulares. El complejo de los esteroides con estos receptores entra al núcleo y altera la transcripción y traslación del DNA. También alteran la síntesis de enzimas. Como resultado hay lisis de la línea linfoide, disminución en la utilización de la glucosa y disminución de la síntesis de DNA, RNA y proteínas. En resumen su acción es múltiple y a diferentes niveles.

Los efectos secundarios también son múltiples; produce alteraciones en el metabolismo de carbohidratos, grasas, y proteínas. Aumentan la retención de sodio y agua y la excreción de potasio. Pueden conducir a hipertensión por la retención de agua. Aumentan la incidencia de infecciones, disminuyen la cicatrización, aumentan la incidencia de perforaciones intestinales y de sangría gastrointestinal. Producen cambios en el sistema nervioso central, en el sistema locomotor y en los vasos sanguíneos. Disminuyen la absorción de calcio, aumentan la incidencia de pancreatitis, producen retraso en el crecimiento, anomalías en el embarazo con aumento en los natimueertos y producen anomalías congénitas en animales experimentales. También aumenta la incidencia de cataratas, glaucoma y exoftalmos. Producen disturbios en el eje hipotálamo-hipófisis-adrenal y producen apariencia Cushinoide. Finalmente pueden producir también reacciones alérgicas.

La globulina antilinfocítica (GAL) es otra forma de afectar los linfocitos y es más específica. Su uso está limitado al presente a trasplante de órganos como terapia inmunosupresora directa en con-

tra de los linfocitos. Mediante el uso del GAL se ha logrado retrasar los episodios de rechazo y reducir su severidad. Recientemente se ha utilizado también para tratar el rechazo con algún éxito. Aunque se pueden utilizar diferentes vías se prefiere la intravenosa pues se reducen las reacciones locales, las cuales pueden ser muy severas. Dentro de las complicaciones se incluyen reacciones alérgicas desde anafilaxis, enfermedad del suero, reacciones de piel, fiebre, escalofríos, depósitos de complejos inmunes en las membranas celulares y otras. También produce trombocitopenia, anemia y linfopenia. Sus dosis deben ajustarse a los niveles de plaquetas que son las primeras en alterarse. Otro problema con la GAL es la variación en su potencia y constitución, que hace difícil comparar resultados en diferentes centros.

Alternativas como el drenaje del ducto torácico y la timectomía han pasado al desuso debido a que son procedimientos invasivos y complicados, y con la GAL se obtienen resultados similares en forma más sencilla. La esplenectomía inicialmente utilizada por Starzl y por Hume ha vuelto a resurgir, al probar su efectividad en trasplante de riñón, prolongando la sobrevida del injerto en un 15-20 por ciento. Otra forma de reducir los linfocitos es por medio de la radiación en la cual también se ha visto un resurgir reciente. Esta puede ser corporal total, usada principalmente en trasplante de médula; o local, que es la que se usa más en trasplante de riñón para destruir los linfocitos activados dentro del injerto durante el episodio de rechazo. Recientemente se ha enfatizado la importancia de transfusiones preoperatorias, como una alternativa para la producción de inmunosupresión por medio de anti-

cuerpos bloqueadores.

Una nueva droga, la Ciclosporina A, es un extracto de los hongos "*Cylindrocarpon lucidum*" y "*Trichoderma polysporum*" descubierto por Dreyfuss y caracterizado bioquímicamente por Ruegger y Petcher para 1976. En el 1976 Borel encontró acción inmunosupresora deprimiendo tanto la inmunidad humoral como la celular, aunque es más efectiva en contra esta última. Calne la ha evaluado en humanos en trasplantes de riñón, páncreas e hígado, y Starzl ya ha reportado éxito en transplante de riñón, utilizando mucho menos esteroides y con resultados mejorados. Sin embargo, la ciclosporina no está libre de complicaciones y ha demostrado toxicidad hepática y renal significativa. Hasta el presente no ha demostrado toxicidad a la médula ósea y por lo tanto ha minimizado el riesgo de infecciones que conllevan otros agentes inmunosupresores. Otros efectos secundarios producidos por la ciclosporina son hirsutismo en menor grado, hiperplasia de las encías y una incidencia más alta de linfomas intestinales. Las dosis usuales son de 17.5mg/kg/d, pero se reducen a 10mg/kg/d si produce daño hepático o renal.

Todo paciente inmunosuprimido tiene ma-

yor incidencia de infecciones y cáncer. Una incidencia de cáncer nuevo de 6 por ciento es mayor a la de la población en general, y una incidencia de metástasis en cáncer preexistentes de 36 por ciento, es también mayor. De los cánceres más comunes son los de piel, tejido linfóide, y epiteliales. Es de notar la alta incidencia de malignidad cerebral que es muy raro en la población en general. Todo paciente en inmunosupresión debe tener un examen físico orientado a la detección del cáncer cada 3-6 meses.

La causa principal de muerte en personas inmunosuprimidas son las infecciones en especial por organismos oportunistas. La única forma de prevenir la muerte en estos pacientes es mediante procedimientos de diagnóstico agresivos y tempranos de forma que se evite la diseminación y establecimiento de la infección. Además es importante tener claro los criterios para detener la inmunosupresión antes de que ésta termine con la vida del paciente.

He presentado un cuadro superficial del uso de los inmunosupresores, subrayando sus complicaciones para indicar la necesidad de mantenerlos alerta. No obstante, si se utilizan las guías indicadas, su uso puede ser menos peligroso, y ayudar a mejorar los resultados de la terapia supresores.

CAN WE VACCINATE AGAINST SCHISTOSOMES? AN UPDATE FIVE YEARS LATER

George V. Hillyer, PhD

Summary: This review attempts to summarize the work done on immunity to schistosomes using antigens of *Fasciola hepatica* during the 5 years following our original article published in this *Boletín*. Among our findings have been the following: the protective *F. hepatica* antigens were those which bound to antibodies to *Schistosoma mansoni*. As antigen purification proceeded less amounts were required to obtain significantly high levels of protection. These two factors, cross reactivity and improved protection with increasing antigen purity (and possibly improved immunogenicity) are both supportive of an immunological basis for protection against *S. mansoni*. The protective antigens were found to bind with Concanavalin A suggesting that they were glycoproteins or glycolipids and a major peak eluted from Concanavalin A appeared to have an isoelectric point in the range of 4.0-4.4. Mice immunized with *F. hepatica* antigens developed antibodies to *S. mansoni* and those immunized with *F. hepatica* followed by infection with *S. mansoni* developed higher antibody levels to *S. mansoni* than unimmunized-infected controls. This observation again supported the concept that the protective effect was due to cross-reactive antigens which then induced an anamnestic immunologic response. Immunity was expressed as reduction in *S. mansoni* worm burdens in vaccinated versus control groups after challenge with *S. mansoni* cercariae, and was as high as 83 percent. However, an additional effect was observed in that

female schistosome worms in immune mice had impaired egg laying capacity. This suggested that the vaccine had an anti-fecundity effect. Since the host response against eggs results in granulomatous hypersensitivity and pathology, the vaccine could be interpreted as having an anti-pathology effect. The protective antigens have been located on the tegument surface of schistosome and *Fasciola* worms. These antigens are probably shed continuously during infection and may explain in part why infection with one parasite induces resistance to challenge with a different trematode parasite.

Introduction

Five years ago this month (December) we reported on a new approach to the study of immunity to schistosomes (1). In that report we demonstrated that mice immunized repeatedly with subcellular extracts of *Fasciola hepatica* worms and challenged with cercariae of *Schistosoma mansoni* developed significantly less worms than normal controls.

The rationale for the study at that time included the following:

- a. It was generally conceded that homologous schistosome subcellular fractions were ineffective vaccines (2).
- b. Animals infected with other schistosome species were partially resistant to challenge exposure with *S. mansoni* cercariae (3). Thus cross-protection among schistosomes was evident.
- c. The eosinophil had been shown to

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TABLE I

**Summary of *Fasciola hepatica* Adult Worm Antigen Preparations
Used for the Immunization of Mice followed by
Challenge Infection with *Schistosoma mansoni* Cercariae**

Antigen	Preparation	References
FhWWE	Fresh worms obtained from bovine livers, homogenized, lyophilized, weighed as dry powder, reconstituted in buffer. Amounts expressed as dry weight.	Hillyer et al, 1975
Fh _{Sm}	FhWWE eluted with acid from column containing anti- <i>S. mansoni</i> IgG coupled to CNBr Sepharose 4B. Amounts expressed as protein (Lowry)	Hillyer, 1976; Hillyer et al, 1977
Fh _{SmIII}	Fh _{Sm} separates into three peaks when chromatographed through columns containing Sephadex G-200. Fh _{SmIII} is the last peak eluted. Amounts expressed as protein (Lowry).	Hillyer et al, 1977
Fh _{SmIII(M)}	A major antigen in Fh _{SmIII} . Antibody is prepared by combination of Laurell crossed electrophoresis and affinity chromatography. Antigen is purified from FhWWE by elution with acid from column containing anti-Fh _{SmIII(M)} IgG coupled to CNBr-Sepharose 4B. Amounts expressed as protein (Lowry).	Hillyer and Cervoni, 1978
Fh _{Con A (E1-1)}	FhWWE eluted from Con A Sepharose 4B with alphanethyl glucoside. Amounts expressed protein (Lowry).	Hillyer and Sagramoso de Ateca 1979;
Fh (pI 4.2)	FhWWE submitted to isoelectric focusing. The peak having an isoelectric point of 4.2. Amounts expressed as protein (Lowry).	Hillyer et al, 1981 in preparation
Fh _t	<i>F. hepatica</i> tegument antigens, obtained by incubation of fresh worms in 1 percent Nonidet P-40, the supernate after centrifugation at 50,000 g for 4 hours. Amounts expressed as protein (Lowry).	Hillyer, 1980.

TABLE II

Summary of Immunity Experiments in Mice with Crude of
Fasciola Hepatica Antigens Followed by
Challenge with *Schistosoma Mansoni* Cercariae

Antigen	No. of Inocs.	Total Dose Antigen	Percent Red.	Mouse Strain	Reference
FhWWE	12	6.0 mg	42	CF-1	Hillyer et al 1977
	9	9.0 mg	30	CF-1	Hillyer et al 1975
	9	4.5 mg	49	CF-1	Hillyer 1976
	9	4.5 mg	50	CF-1	Hillyer et al 1977
	9	4.5 mg	65	CBA-J	Hillyer et al 1977
	9 (s.c.)	4.5 mg	62	CBA-J	Hillyer et al 1977
	9	4.5 mg	28	CF-1	Hillyer, 1979
	9	4.5 mg	40	CF-1	Hillyer, 1979
	9	4.5 mg	32	NIH(GP)	Hillyer, 1979
	9	9.0 mg	54	CF-1	Hillyer, 1979
	9	4.5 mg (+1X poly AU)	67	CBA-J	Hillyer, 1979
	9	4.5 mg (+2X poly AU)	72	CBA-J	Hillyer, 1979
	6	3.0 mg	0	CF-1	Hillyer et al 1977
	6	3.0 mg	52	CBA-J	Hillyer et al 1977
	3	1.5 mg	39	CF-1	Hillyer et al 1977
	3	1.5 mg	46	CBA-J	Hillyer et al, 1977
	3	4.5 mg	0	CF-1	Hillyer, 1979
	3	3.0 mg	17	CF-1	Hillyer, 1979
	3	9.0 mg	0	CF-1	Hillyer, 1979
	1	4.5 mg	0	CF-1	Hillyer, 1979
Fh _{Sm}	9	270 ug	46	CF-1	Hillyer, 1976
	9	56 ug	57	NIH(GP)	Hillyer, 1979
	9	112 ug	60	NIH(GP)	Hillyer, 1979
	9	225 ug	8	NIG(GP)	Hillyer, 1979
Fh _{SmIII}	9	112 ug	49	CF-1	Hillyer, 1977
	9	68 ug	50	CF-1	Hillyer, 1977
Fh _{SmIII(M)}	9	3.0 ug	62	NIH(GP)	Hillyer, 1979
	9	3.0 ug (+1X poly AU)	81	NIH(GP)	Hillyer, 1979
Fh _{ConA(E1-1)}	9	22 ug	68	NIH(GP)	Hillyer & Sagramoso, 1979
	9	22 ug	54	NIH(GP)	Hillyer & Sagramoso, 1979
	9	4.5 ug	68	NIH(GP)	Hillyer & Sagramoso, 1979
	9	45 ug	60	NIH(GP)	Hillyer & Sagramoso, 1979
	9	4.5 ug	30	NIH(GP)	Hillyer & Sagramoso, 1979
	9	4.5 ug	28	NIH(GP)	Hillyer & Sagramoso, 1979
	9	0.45 ug	37	NIG(GP)	Hillyer & Sagramoso, 1979
	9	0.45 ug	21	NIH(GP)	Hillyer & Sagramoso, 1979
Fh _{pl 4.2}	3	3 ug	74	NIH(GP)	Hillyer, 1981 (this paper)
Fh _t	1	30 ug	51	NIH(GP)	Hillyer, 1981 (this paper)
	1	30 ug	23	CBA/J	Hillyer & Serrano, 1981
	1	30 ug	47	CBA/J	Hillyer & Serrano, 1981
	3	90 ug	42	CBA/J	Hillyer & Serrano, 1981
	3	90 ug	83	CBA/J	Hillyer & Serrano, 1981

be a killer cell in schistosome infections (4).

- d. Fascioliasis was known to induce a high level of eosinophils in man (5).
- e. *Fasciola* and *Schistosoma* worms shared common and/or cross-reactive antigens (6).

The following is a summary of the work related to this experimental vaccine. The designation given to the different antigen preparations used for immunization is summarized in Table I. A summary of most of the immunity experiments and their references is found in Table II.

Early Studies

Our first studies were designed to demonstrate that crude extracts of *F. hepatica* (designated FhWWE) could induce protection in mice and hamsters to a challenge infection with *S. mansoni* cercariae. An added control was the use of a nonspecific immunogen, bovine serum albumin (BSA). Since FhWWE was obtained from infected cattle, BSA was an expected contaminant and its possible protective effect had to be ascertained. The standard protocol involved multiple inoculations over a period of 3 weeks, resting the mice one week, and then challenging them with *S. mansoni* cercariae percutaneously. In the first reported experiment in mice, a 30 percent worm burden reduction was obtained in mice immunized with FhWWE and only 12 percent in those immunized with BSA. Thus the parasite antigen was a better protective antigen than BSA. This was confirmed in hamsters in which 14 and 27 percent worm burden reductions were obtained in the groups immunized with FhWWE as compared to the BSA controls (1).

In our early work we had observed that the FhWWE antigens which cross-reacted with antibodies to *S. mansoni* adult worms appeared in the descending portion of the first peak when chromatographed through Sephadex G-200 (1). This suggested that they were in the 150,000 - 200,000 MW range (reviewed in reference No. 7). A pool was made

of the fractions obtained from the Sephadex G-200 chromatography of FhWWE which contained the cross-reactive antigens and mice were immunized with this pool. To our elation a 39 percent reduction in worm burden was found in the immunized mice after challenge with *S. mansoni* (1). This suggested to us that the protective antigens in FhWWE could be those which cross-react with *S. mansoni*.

To test the hypothesis that the effective FhWWE antigens were those cross-reactive with *S. mansoni* worms we resorted to the technique of antibody-affinity chromatography. In this technique the IgG fraction of the rabbit serum containing the antibodies to *S. mansoni* worms was isolated and covalently coupled to CNBr-Sepharose 4 B. Thus when FhWWE was added to a column containing the above, the cross-reactive antigens linked to the antibody and those which did not filtered through the column and appeared in the drop through. The antigen-antibody complex was then dissociated, and the cross-reactive antigens were then eluted in a separate fraction pool. This pool of antigens was designated Fh_{Sm}. The results were presented in 1976 at the annual meeting of the American Association of Immunologists and summarized in a subsequent review (8, 9). The results were impressive in that mice immunized with Fh_{Sm} or FhWWE had 46-49 percent reduction in *S. mansoni* worm burdens over controls. In hamsters immunized with FhWWE or Fh_{Sm} the percent immunity was 25 and 50 percent respectively. Mice or hamsters treated with the drop through (see above) containing for the most part the non-crossreacting antigens had 24 to 0 percent reduction in worm burdens. The importance of these studies was that we demonstrated for the first time that the *F. hepatica*/*S. mansoni* cross-reactive antigens were the ones responsible for the protection and that those which were not cross-reactive did not protect.

In a subsequent study further purification of Fh_{Sm} was done using Sephadex G-200 and three peaks were eluted from the gel filtration column. Starting with the void volume, the peaks were denoted Fh_{SmI}, Fh_{SmII}, and Fh_{SmIII}. The best protective antigen was found in Fh_{SmIII} with 49 percent reduction in worm burdens over controls. This population of antigens eluted out of Sephadex G-200

in the 60,000 MW range. In this same study we also demonstrated that hamsters immunized with Fh_{Sm} were significantly protected (57 percent immunity) to infection with *S. mansoni* and that lower concentrations of antigen (FhWWE) and/or numbers of immunizations, could lead to significant protection. Finally, it was shown that mice immunized with *F. hepatica* antigens and infected with *S. mansoni* for 6 weeks had higher antibody titers to *S. mansoni* adult worms (by passive hemagglutination) than infected, but not immunized, controls. This suggested that the *S. mansoni* infection was inducing an amnestic antibody response to the *F. hepatica*/*S. mansoni* antigens (10). Finally, it was clear that as the antigens were purified, less amounts were required to induce significant protection.

Also in 1975 we were initiating studies on the serodiagnosis of fascioliasis (reviewed in reference No. 11) and it became of interest to see whether mice infected with *F. hepatica* would be resistant to a challenge infection with *S. mansoni*. Mice were infected with one cyst of *F. hepatica* and infected with *S. mansoni* 9 weeks later. This time period was chosen because our own studies showed that mice would have high levels of anti-*F. hepatica* antibodies at that time. The results showed a 56 percent *S. mansoni* worm burden reduction in the combined infection experimental group over sex and age matched controls (9). Not included in that report were 5 mice given the *F. hepatica* cysts but in which the infection did not develop. When those mice were infected with *S. mansoni* their worm burdens at necropsy were identical to the controls. These studies suggested that the *F. hepatica* antigens inducing the protection were being excreted by the worm, possible as metabolic antigens or shed as tegument antigens. Parasitic trematodes have been shown to turn over rapidly tegumental layers (11) and, in the case of *F. hepatica*, the type of antigen on its surface changes with the age of the parasite (13, 14). Our finding that an infection of *F. hepatica* confers protection to challenge infection with *S. mansoni* was amply confirmed by Christensen and collaborators (15).

Isolation of a Pure Antigen

Parasite trematodes are extremely complex.

A rabbit hyper-immunized with FhWWE was found to produce over 56 precipitating antibodies when reacted by Laurell crossed immunoelectrophoresis (16). The complexity was reduced significantly with Fh_{Sm}. Thus when FhWWE was reacted with an anti-*S. mansoni* adult worm rabbit serum by Laurell crossed immunoelectrophoresis only a dozen arcs of precipitation were seen (16). The number of arcs was reduced in half (to 6) when FhWWE was reacted with an anti-Fh_{SmIII} serum by Laurell crossed immunoelectrophoresis, again simplifying even more the system (17). As reported above, Fh_{SmIII} also was shown to contain the Fh_{Sm} antigens which protected mice to challenge with *S. mansoni*. We noted the presence of a major arc of precipitation in the Laurell crossed immunoelectrophoresis pattern of FhWWE vs. anti Fh_{SmIII}, and were able to purify the antigen. This was done by producing a monospecific antibody to the antigen by rabbit immunization, coupling the IgG containing the antibody to CNBr-activated Sepharose 4B, adding to the mixture FhWWE and discarding the drop through, and eluting the antigen with acid buffer. This antigen was designated Fh_{SmIII(M)} (17). Inoculation of mice with less than 3 µg protein of this pure antigen (in 9 doses of 300 ng each) resulted in a 62 percent reduction of *S. mansoni* worm burdens as compared to controls (16). Although the worm burdens of the controls were also low, the results confirmed the trend that as the antigen became increasingly purified, the less the amount required to produce significant levels of immunity. In this last paper (16) additional confirmatory experiments showed that the sequence of antigen purification from FhWWE to Fh_{Sm} to Fh_{SmIII} to Fh_{SmIII(M)} all retained the protective antigens while the amount of antigen required for protection decreased at each step in the purification. However, it appeared that either multiple inoculations or a one month sensitization phase from the time of the first immunization were required for maximum protection. Of additional interest was that the B-cell adjuvant, polyadenylic-polyuridylic (poly AU) acid, alone induced significant levels of protection (56 percent immunity to challenge with *S. mansoni* (16, 18). When poly AU was used in combination with Fh_{SmIII(M)} the *S. mansoni* worm burden reduction was an impressive 81 percent. Interestingly, in a study by Maddison et al (19), when

freshly ground *S. mansoni* worms were used to immunize mice to challenge with *S. mansoni* cercariae no protection was observed. When poly AU (using our protocol) and *S. mansoni* worm extracts were used as immunogens a 32 percent reduction in worm burdens was obtained.

Isolation of *F. Hepatica* Glycoproteins

The approach of isolating and purifying the *F. hepatica*/*S. mansoni* cross-reactive antigens by antibody affinity chromatography was necessary to continually demonstrate that the protective effect was in fact an immunologically specific one, and that the shared antigens were the important ones. If small amounts of antigen are required, then this approach is indeed acceptable. However, obtaining large amounts of antigen by antibody affinity chromatography is impractical and costly. This led to a second approach (suggested by Ronald P. Pelley, then at Case Western Reserve University) which was to initiate the purification process of FhWWE by Concanavalin A (Con A) affinity chromatography. The rationale for this approach was the observation that Fh_{Sm} had approximately a 2:1 carbohydrate to protein ratio and were thought to be glycoproteins (9).

When FhWWE was chromatographed through Con A Sepharose 4B two peaks appeared in the drop through (DT-1, DT-2). The bound antigens were then eluted with alpha-D-methylglucoside and the eluate was designated Fh_{Con A} (E1-1). In the initial immunity experiment reported at the 1978 meeting of the American Society of Immunologists DT-1 induced marginal immunity (30 percent) and DT-2 (81 percent) and E1-1 (68 percent) induced significant levels of immunity (20). In the duplicate experiment both DT-1 and DT-2 induced lower immunity (25 and 39 percent, respectively) than E1-1 (54 percent). Combining DT-1 and DT-2 and used at 3 log-dose concentrations in two experiments resulted in 14-29 percent reduction in *S. mansoni* worms recovered. However, a total antigen dose (protein) of 5 ug of Fh_{Con A} (E1-1) inoculated each of 9 times resulted in 60-68 percent less *S. mansoni* worms recovered as compared to controls. Lower doses

of antigen resulted in less protection, with 21-37 percent immunity being the range (21).

It was clear that Fh_{Con A} (E1-1) would induce protection in mice to infection with *S. mansoni* and was superior in most experiments to DT-1 and DT-2. In examining for correlates to our previous work, Fh_{Con A} (E1-1) was further fractionated by isoelectric focusing and each fraction collected was reacted with a variety of antibodies developed in rabbits to the *F. hepatica* antigenic preparations shown to induce immunity to *S. mansoni* in mice. Although the isoelectric focusing profile at 254 and 280 nm showed 6-7 peaks, a major peak with a pI range of 4.0 - 4.4 (average = 4.2) was observed. It was with this peak that the antisera to Fh_{Sm}, Fh_{SmIII}, and Fh_{SmIII(M)} reacted (21). This clearly showed the interphase between the previous antigens purified by antibody affinity chromatography and gel filtration, and the antigens purified by Con A. It also demonstrated the viability of a large scale first purification step utilizing Con A. Finally, it showed that the important antigen(s), with their pI of 4.2, could conceivably be isolated by large-scale preparative isoelectric focusing (see THE pI 4.2 ANTIGENS).

Solubilization and Stability

From our very initial studies we knew that the *F. hepatica*/*S. mansoni* cross-reactive antigens in FhWWE appeared in the first peak after gel filtration in Sephadex G-200 suggesting a MW in the 150,000-200,000 range (1). However, when Fh_{Sm} was obtained from FhWWE by antibody affinity chromatography and then filtered through Sephadex G-200 three peaks were obtained, two of which were of less than 150,000 MW (9, 10). A third observation was that when FhWWE, solubilized in PBS, was centrifuged at 10,000 g for 15 min, and the supernate used to immunize mice, no protection was obtained to a challenge infection with *S. mansoni* (Hillyer and Del Llano de Díaz, unpublished). This suggested that the antigens of *F. hepatica* reactive with *S. mansoni* were largely particle or membrane bound, and that saline extraction was largely inefficient. This was

shown by extracting FhWWE in phosphate buffered saline (PBS) followed by low-(500 g) and high-speed (10,000 g) centrifugation. At low speed centrifugation the supernate antigen reacted weakly with an anti-*S. mansoni* worm rabbit serum. High speed centrifugation resulted in a 40 percent loss of protein in the supernate (as compared to supernate obtained by low speed centrifugation) and, in addition, loss of reactivity to the anti-*S. mansoni* worm rabbit serum. Addition of low amounts of detergent (sodium dodecyl sulfate) to the PBS followed by high speed centrifugation resulted in a significant increase in antigenic reactivity to the *S. mansoni* antiserum (7). Thus it was clear that use of detergent increased significantly the efficiency of the extraction. In addition, the elution profiles of FhWWE solubilized in PBS and detergent showed that the *F. hepatica*/*S. mansoni* cross-reactive antigens liberated by the detergent were largely materials under 200,000 MW and over 60,000 MW (7).

In subsequent studies we demonstrated that at the low concentrations of detergent used (0.005 percent) the precipitation assays used to monitor the presence of cross-reactive antigens were unaffected (22). We also observed that the acid treatment significantly affected the antigenic reactivity of FhWWE when reacted with an anti-*F. hepatica* serum. However, it did not affect the reactivity of a major antigen in FhWWE which cross-reacted with the anti-*S. mansoni* serum. Thus if this is the protective antigen, its ability to withstand harsh treatment is significant in that it could be transported to less developed areas of the world without losing its immunogenicity.

Cross Reactivity

Using Ouchterlony immunodiffusion the presence of a common antigen between *S. mansoni* eggs and *F. hepatica* worms using an anti-*S. mansoni* adult worm antiserum was shown. It was different from the three major serologic *S. mansoni* egg antigens (23). When rabbit sera to *S. mansoni*, *S. japonicum*, and *F. hepatica* worms were reacted by Ouchterlony immunodiffusion with FhWWE one precipitation line

was found which linked with each of three sera suggesting a common antigen between the three species (16). This suggests that an *F. hepatica*/*S. mansoni* cross-reactive antigen may also be an *F. hepatica*/*S. japonicum* cross-reactive antigen. If it is the protective antigen in the *S. mansoni* model it may conceivably also protect to a challenge infection with the Oriental species of schistosome. By Laurell crossed immunoelectrophoresis 9-12 arcs of precipitation were seen when *F. hepatica* antigen was reacted with an anti-*S. japonicum* serum (16).

Mice infected with *F. hepatica* for only 3 weeks developed antibodies to *S. mansoni* soluble egg antigen when tested by ELISA. Mice infected with *S. mansoni* for 7 weeks developed precipitating antibodies to FhWWE when tested by Ouchterlony immunodiffusion (24). We have clearly shown that a large proportion of human infected with *S. mansoni* react with *F. hepatica* worm antigens (by counterelectrophoresis) and that a large proportion of humans infected with *F. hepatica* react with *S. mansoni* SEA by ELISA (25, 26). This cross-reactivity is of obvious diagnostic importance in that use of crude extracts for serodiagnosis will result in a large proportion of false positive reactions. However, it may also be that some of the protective antigens are shed from the parasite's tegument. It was already shown that mice infected with *F. hepatica* acquire resistance to infection with *S. mansoni* (9). Recently we showed that mice infected with *S. mansoni* for 5 (but not 3) weeks were significantly resistant to challenge infection with *F. hepatica* (27). Thus this resistance works in both directions and may occur between other parasitic trematodes as well.

The mechanism for this resistance is unknown, but the evidence points to its being at least in part immunological. Thus the most logical place to then look for the parasite antigens was on the tegument.

Fasciola Tegument Antigens

For the immunity studies done previously where subcellular antigens were used, the starting material was a whole worm extract of *F. hepatica* (FhWWE) with its obvious antigenic complexity. We

then decided to isolate only the *F. hepatica* tegument antigens (Fh_t) by incubation of freshly collected worms in 1 percent of the nonionic detergent Nonidet P-40 in PBS at 4°C. The liquid was centrifuged at 50,000 g to obtain in the supernate the soluble antigens which were then concentrated by vacuum dialysis against PBS. When this was done it was clear that an important genus-specific immunodiagnostic antigen was obtained. But, in addition, the antigens released included antigens reactive with sera prepared against $Fh_{Con A}$ (E1-1) and $Fh_{SmIII(M)}$ (28). That these antigens are truly only on the surface of the *F. hepatica* worm was shown by light microscopy using a peroxidase-antiperoxidase immunocytochemical method (28). In addition to being on the *F. hepatica* worm surface they were also shown to be on the surface of *S. mansoni* male and female worms by immunoelectron microscopy (29). This further sup-

ported the working hypothesis that the *Fasciola/Schistosoma* cross-reactive antigens which induce acquired immunity to challenge infection with *S. mansoni* were tegument antigens. But did they in fact protect?

In a first attempt to answer this question, a single 30 microgram dose of Fh_t emulsified in Freund's complete adjuvant was administered to each of 10 NIH (GP) mice. Both this group, as well as the controls, were infected 4 weeks later with *S. mansoni* cercariae and killed 6 weeks afterwards for the determination of worm burdens. As can be seen in Figure 1, a 51 percent reduction in worm burden was obtained in the immunized group.

Two additional protection experiments using Fh_t have been done and 23-47 percent reductions in *S. mansoni* worm burdens were obtained with one inoculation, and 42-83 percent *S. mansoni* worm burden reductions were obtained with 3 inoculations. These studies clearly demonstrated that *F. hepatica* tegument antigens protected mice to challenge infection with *S. mansoni* cercariae (30).

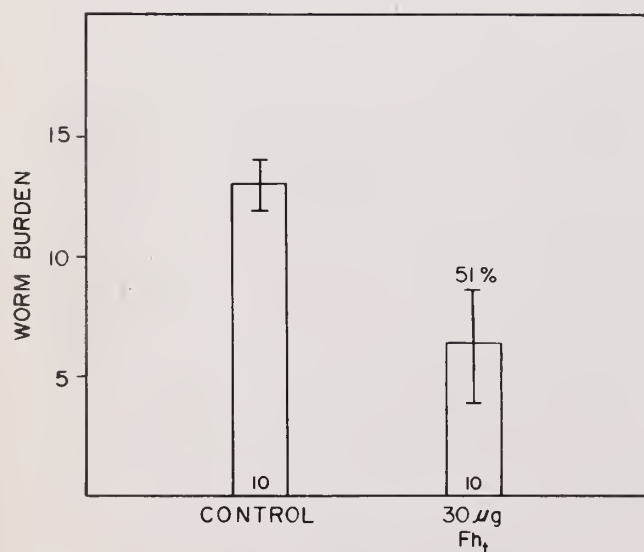


Figure 1: Effect of a single inoculation of 30 micrograms of *Fasciola hepatica* tegument antigen (Fh_t) emulsified in Freund's complete adjuvant on challenge exposure with *Schistosoma mansoni* cercariae 4 weeks later. Numbers of mice per group are indicated on the bar graph. Note that this single vaccine dose resulted in a 51 percent worm burden reduced in the immunized group as compared to the adjuvant controls.

The pl 4.2 Antigens

We had previously demonstrated that the protective effect of *F. hepatica* antigens resided in the fraction which bound to Concanavalin A and which was subsequently eluted with alpha-methyl glucoside (20, 21). When this fraction (denoted $Fh_{Con A}$ (E1-1)) was further separated by isoelectric focusing a large peak with an isoelectric point range of 4.0-4.4 (average 4.2) was obtained. Ouchterlony immunodiffusion using various antisera against this peak showed that this peak contained the *Fasciola/Schistosoma* cross-reactive antigens including $Fh_{SmIII(M)}$ (21) and was denoted the pl 4.2 peak.

To see whether this pool of antigens were also effective immunizing agents NIH female outbred albino mice were inoculated i.p. with 1 μ g of $Fh_{pl 4.2}$ antigen emulsified in Freund's complete adjuvant. One month later they were inoculated with 1 μ g of $Fh_{Con A}$ (E1-1) in Freund's incomplete adjuvant. The third inoculation one month afterwards was with 1 μ g $Fh_{pl 4.2}$ in incomplete ad-

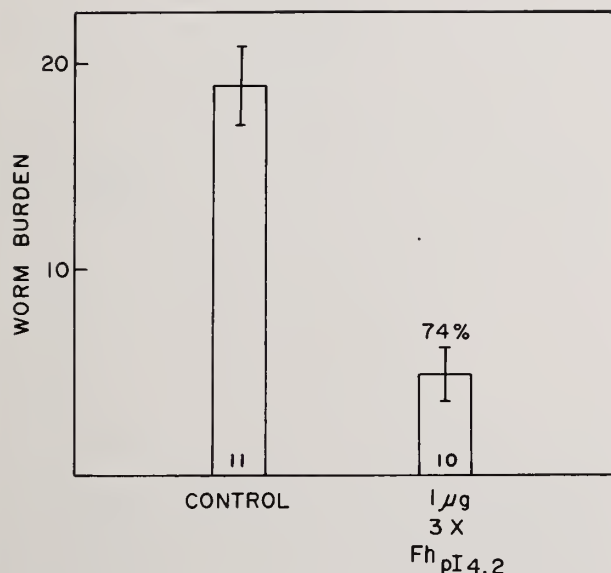


Figure 2: Effect of multiple inoculations of *Fasciola hepatica* pI 4.2 antigen preparation on challenge exposure with *Schistosoma mansoni* cercariae (See text). A significant 74 percent reduction in worm burdens was obtained in the immunized mice as compared to controls.

juvant with challenge to *S. mansoni* cercariae done one month after the third immunization. As can be seen in Figure 2 a significant 74 percent reduction in worm burdens was obtained in the immunized mice as compared to the controls. These results also demonstrated that minute amounts of purified *F. hepatica* antigen can induce significant levels of protection in mice to a challenge infection with *S. mansoni* cercariae.

The Anti-Fecundity Effect

We had long observed that mice immunized with *F. hepatica* antigens and infected with *S. mansoni* appeared at necropsy to have few granulomatous lesions in their livers. One method of quantifying this observation is by counting the *S. mansoni* eggs in livers digested with KOH according to the method of Cheever (31). Figure 3 summa-

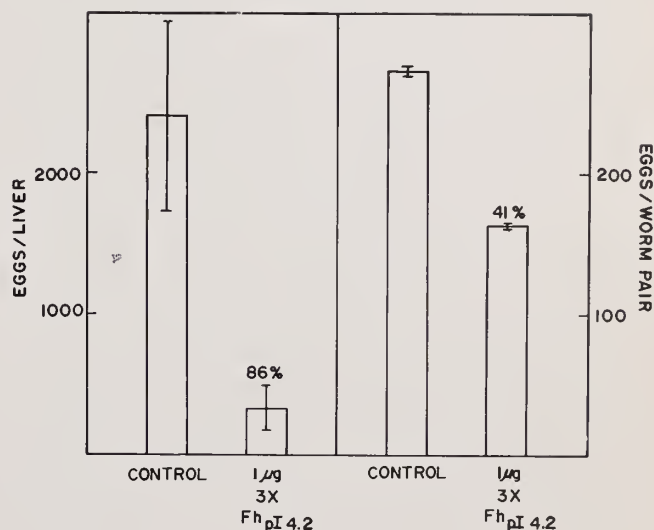


Figure 3: Apparent anti-fecundity effect of *Fasciola hepatica* pI 4.2 antigen on the production of eggs by *Schistosoma* female worms as reflected in egg counts obtained from mouse livers. Note that although the pI 4.2 antigen induced a 74 percent reduction in *S. mansoni* worms recovered the egg load reduction was even higher (86 percent). Adjusted to eggs per worm pair the reduction was still 41 percent. This suggests that the vaccine, in addition to reducing worm loads, also reduces egg loads suggesting an anti-fecundity effect.

zes the liver egg loads of mice immunized with pI 4.2 antigen described above. Although the worm burden reduction was 74 percent, the egg load reduction was 86 percent. Since the female *S. mansoni* worms lay the eggs, the results were normalized to reflect egg burdens per worm pair. Even with this adjustment, the liver egg load per worm pair was 41 percent less than the control. This suggested that the vaccine also affected the egg laying capacity of the female parasite.

This was confirmed by immunizing mice with *F. hepatica* tegument antigens. When immunized once with 30 µg Fh_t and challenged with *S. mansoni* cercariae 4 weeks later, a 47 percent reduction

in worm burden was obtained. However, in the immunized group there was a 69 percent decrease in *S. mansoni* eggs per liver (35 percent decrease when adjusted to per worm pair). When 3 immunizations were used, worm burden reduction was 83 percent, but the percent reduction in the livers of the immunized mice was an even greater 94 percent (80 percent reduction per worm pair) (30). These results again suggested that the *F. hepatica* antigens, in addition to inducing immunity to challenge with *S. mansoni* expressed as reductions in worms recovered also appeared to exert an additional effect on the female parasite as expressed in the numbers of eggs found in the livers of infected mice. Since *S. mansoni* eggs are involved in the host's granulomatous response (32), any diminution in the number of eggs produced should also result in a diminution of pathology.

Acquired Resistance in Schistosomiasis

The subject of immunization against schistosomes is currently being approached in various ways. Non-specific immunoadjuvants such as bacille Calmette-Guerin, *Corynebacterium parvum*, poly AU, and natural cord factor have all been shown useful in the development of acquired resistance (16, 19, 33). The use of radiation attenuated cercariae and schistosomules as experimental vaccines in schistosomiasis *mansoni* have been known for almost two decades (34, 36). In fact, regarding a bovine schistosome, *S. bovis*, field trials using the homologous schistosomular irradiated vaccine have yielded impressive results with 60-70 percent reductions in worm and tissue counts in vaccinated calves as compared to those not vaccinated (37). However, live vaccines involve exposure to infection and this approach is less appealing for their use in man.

Our approach has been to isolate the common and/or cross-reactive *Fasciola/Schistosoma* antigens. Why, then, don't schistosome extracts generally protect, while the scientific literature is replete with articles showing that a primary infection with *S. mansoni* at least partially protects animals to a challenge infection with the same parasite? One

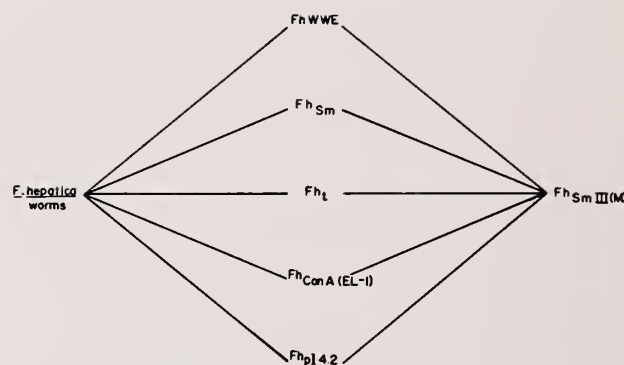


Figure 4: This summarizes five different approaches to isolating *F. hepatica* antigens from worms which have been shown to protect mice to challenge infection with *S. mansoni* cercariae. Note that all five isolation procedures all result in antigen preparations which contain Fh_{SmIII(M)} which has been shown to be a protective antigen.

possibility is that the protective antigens are in insufficient amounts and that their continuous release, possibly from the parasite tegument, results in an anamnestic response which slowly builds up immunity. The antigens found in extracts may not be in the proper form for optimal stimulation and may be poorly immunogenic. Finally, the possible presence of antigens which suppress the immune response and inhibit the development of acquired immunity must be considered.

Smithers and Miller recently demonstrated that there are probably two distinct mechanisms responsible for the killing of schistosomes in mice. The first is an early phase which occurs in the skin. The second is a late phase occurring at 6-14 days post-infection after the lung phase and occurring either in the systemic circulation or immediately upon arriving in the liver (38). This suggests that a single "magic bullet" antigen vaccine will probably not be sufficient for full protection. Whether our isolated antigens are responsible for early or late stage protection still remains to be determined. The effectiveness of these antigens on other challenge infec-

tion with other schistosome species and even other trematode parasites, as well as the mechanisms involved in this protection, are to be determined. The observation that infections with one trematode species protect against challenge infection with a different trematode species makes us wonder whether this is a more generalized phenomenon. Leads to study these areas are currently under way.

Concluding Comments

It is obvious that we are still far away from a practical vaccine for use in man. However, the research effort described herein is a distinct approach to investigating an experimental vaccine using subcellular antigenic extracts. *F. hepatica* worms can be obtained in large amounts and inexpensively. *S. mansoni* antigens are obtainable in comparatively smaller amounts and are more costly.

As diagrammed in Figure 4 there is a common link in all of the isolation procedures between *F. hepatica* adult worms and Fh_{SmIII(M)}. It is probable that two or more *Fasciola*/*Schistosoma* cross-reactive antigens are involved in acquired immunity in *S. mansoni* infections. Efforts are currently underway to identify a second protective antigen. The observation that there are *Fasciola*/*S. japonicum* cross-reactive antigens makes attractive the possibility that some *Fasciola* antigens, may be useful for vaccination against other schistosome species. Studies along these lines are also currently under way.

Acknowledgments

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THE IMMUNOTHERAPEUTIC EFFECT OF A POLYANTIGENIC VACCINE IN ANIMAL TUMOR MODELS

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Angel A. Román Franco, MD
Eduardo A. Santiago Delpín, MD

Immunotherapy of cancer can be defined as any immune procedure that stops, inhibits, or destroys an established tumor (1). The need for immunotherapy in human tumors arises from the fact that: (a) quite often it is impossible to control or destroy a tumor by more conventional means, (b) even the most aggressive therapies often leave behind residual tumor cells, and (c) the immune system alone is unable to cope with tumor growth.

The principal substances being employed today in nonspecific immunotherapy of human tumors in addition to BCG are *C. Parvum* and levamisole. Other common adjuvants include glucan, thymosine and pyran. In animal experiments many more substances have been employed. We are particularly interested in FDA approved bacterial or viral antigens with which man regularly comes in contact and against which a vigorous immunologic response is mounted. Following this criteria a polyantigenic vaccine (PAV) was developed, which consists of a mixture of bacteria and influenza virus in a peanut-oil arlacel-A- aluminum monoesterate emulsions (2).

We will briefly summarize our experiments in the immunotherapy of a variety of tumor systems in different strains of mice. *In vitro* studies on the mechanism of action, done in collaboration with Z. Orraca and E. Ríos-Olivares of the Cayey Medical School, will be reported elsewhere (3).

Materials and Methods

Mice: C₃H/HeJ and Balb/c mice, 12-15 weeks old, were used in these experiments. Food and water were provided ad libitum.

Tumors: Mouse Ehrlich ascites tumor was maintained in serial passage at 3-week intervals in Balb/c mice by intraperitoneal implant. Mouse adenocarcinoma, isolated from C₃H/HeJ mice in this laboratory, was maintained by serial passage at 5-week intervals in C₃H/HeJ mice by subcutaneous implantation.

Preparation of PAV: Peanut Oil and Arlacel A mixed, in a water bath at 60°C, slowly adding the aluminum monoesterate. The mixture is autoclaved for sterility.

Two ml of Fluax (influenza virus vaccine), and 2 ml of bacterial vaccine mixed Respiratory Hollister-Stier Laboratories are added, before each inoculation. The complete system is emulsified with a sterile Multijet syringe system until a pasty consistency is achieved. Aliquots of 0.1 ml of the PAV are used for inoculation.

Results

Growth of Mouse Adenocarcinoma in PAV Treated Mice

Mice were inoculated subcutaneously with 10⁵ CA cells. Treatment with 0.1 ml of PAV per mouse intraperitoneally was started 7 days after tumor implantation and continued once a week thereafter. The tumor size was measured with a caliper with a Vernier scale at the indicated dates and the tumor doubling time was calculated using the Spratt equation. The doubling time growth curve of the tumor in the treated animals behaved in a linear fashion, whereas in the untreated animals showed an

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TABLE I

Tumor take and Survival of Mice Inoculated with Adenocarcinoma Cells
and Treated with PAV

Treatment	N u m b e r o f		Deaths	Tumor-Take %
	Tumor Take	Survivors		
None	14	2	10	87.5
PAV	6	10	0	37.5

P= 0.0035

TABLE II

Survival of Mice Implanted with Adenocarcinoma Cells
and Treated with PAV

Treatment	Deaths	Survivors
None	12	2
PAV	0	6

P= .0004

exponential character.

*Tumor Take and Survival of Mice Inoculated with
Mouse Adenocarcinoma Cells and Treated with PAV*

Thirty-two mice were inoculated subcutaneously with 10^5 adenocarcinoma cells. Treatment with PAV (0.1 ml per mouse intraperitoneally) was started 7 days after tumor implantation and continued once a week for 90 days. The results are depicted in Table I. The control group receiving no treatment showed 87.5 percent of tumor take and 71 percent of the animals died, PAV treated mice showed 37.5 percent tumor take and no deaths (P= .0035).

*Survival of Mice Implanted with Cells and Treatment
with PAV*

Mice of the C₃H strain were inoculated with 10^5 adenocarcinoma cells. Treatment with 0.1 ml of PAV per mouse intraperitoneally was started 7 days after tumor implantation and continued once a week thereafter for 84 days. The results are shown in Table II. Of the untreated mice only 14 percent survived after 84 days, while 100 percent of the mice that were treated with PAV were alive over the same period of time, following tumor implantation (P=.0004).

Survival of Mice Implanted with Chondrosarcoma

TABLE III

Survival of Mice Implanted with Chondrosarcoma Cells
and Treated with PAV

Treatment	Average Day of Death
None	58
PAV	72.6 (50 o/o survivors)
P = .025	

TABLE IV

Survival of Mice Implanted with Ehrlich's Ascites Tumor Cells
and Treated with PAV

Treatment	Deaths	Survivors	o/o Survivors
None	8	1	11.1
PAV	8	10	56.6

P = .027

Cells and Treated with PAV

Twenty C₃H mice were inoculated subcutaneously with 10⁵ chondrosarcoma cells. Treatment intraperitoneally with 0.1 ml per mouse of PAV continued once a week for the duration of the experiment. The treatment with PAV protected from death 50 percent of the experimental mice while all the untreated mice died, with an average day of death of 58 days (Table III) (P=.025).

Survival of Mice Implanted with Ehrlich's Ascites Tumor Cells and Treated with PAV

Twenty-seven mice of strain (Balb/c were inoculated intraperitoneally with 10⁵ Ehrlich's tumor cells. Mice were divided in Group I, which consisted of 9 mice and received no treatment, and Group

2, which consisted of 18 mice and received 0.1 ml. of PAV per mouse (intraperitoneally) two days after implantation and once a week thereafter for sixty days. The untreated group showed 89 percent mortality while the PAV treated group showed only 44 percent mortality (Table IV) (P=0.027).

Growth of Ehrlich's Tumor Cells in the Mice Treated with PAV

Twenty mice strain Balb/c were inoculated intraperitoneally with 10⁵ Ehrlich's tumor cells. Mice were divided in groups of 10 mice. Group I received no treatment, Group 2 received 0.1 ml. of PAV per mouse intraperitoneally two days after tumor implantation and once a week for 4 weeks (total of 5 treatments). Group 3 consisted of 10 mice that received no tumor cells and 0.1 ml. of PAV per mouse.

TABLE V

Survival of Mice Implanted with Chondrosarcoma Cells
and Treated with BCG and PAV

Treatment	Deaths	Survivors	% Survivors
None	27	0	0
BCG (Filtrate)	18	2	10.0
PAV	5	5	50.0
PAV + BCG (Filtrate)	5	7	58.3

se intraperitoneally once a week for 15 weeks. In order to follow the tumor growth, the weight of the animals was taken as an indicator of the amount of ascitic fluid produced. The weight of the mice increased with the amount of ascitic fluid which increased with the amount of tumor cells.

Comparative Survival of Mice Implanted with Chondrosarcoma Cells and Treated with PAV or with BCG

Sixty nine C₃H/HeJ mice were inoculated intraperitoneally with 10⁵ chondrosarcoma cells. The animals were divided in four groups. Group I consisted of 27 mice with no treatment; Group 2 consisted of 20 mice and received 0.2 ml. of a filtrate of a 9-day culture of *mycobacterium bovis* strain BCG per course; Group 3 consisted of 10 mice and received 0.1 ml of PAV per mouse intraperitoneally; Group 4 consisted of 12 mice and received 0.1 ml of a 1:1 mixture of PAV and BCG culture filtrate. The indicated treatment was started 7 days after tumor implantation and continued once a week for the duration of the experiment. The results are shown in Table V. The BCG filtrate alone only protected 10 percent, PAV 50 percent and the mixture 58 percent.

Protection by Individual Components of the PAV

Forty-eight mice strain Balb/c were inocu-

lated intraperitoneally with 10⁵ Ehrlich's tumor cells. The mice were divided into six groups, Group I received no treatment; Group 2 received the virus component of PAV; Group 3 received the bacteria component of PAV; Group 4 received 1/1,000 dilution of the virus + bacteria components of PAV; Group 5 received saline and Group 6 received full strength (undiluted) PAV. All the components were inoculated in a peanut-oil-arlacel-A aluminum monoestrated emulsion, 0.1 ml per animal, intraperitoneally. The virus component was the most effective of the individual components of PAV in protecting mice. This was followed by the bacterial components. The complete PAV was the most effective. (Table VI).

Discussion

The purpose of this study was to determine the efficacy of PAV in different animal tumors systems. The growth of established adenocarcinoma in C₃H/HeJ mice was significantly delayed. Furthermore, PAV was very effective protecting mice implanted with adenocarcinoma cells. The control group receiving no treatment showed 87.5 percent of tumor take and 71 percent of the animals died during the observation period, whereas only 37.5 percent of the PAV treated mice developed tumors and none of the animals died during observation period.

TABLE VI

Protection by Individual Components of PAV

Treatment	Average Day of Death
None	20.1
Virus Component in Emulsion *	29.4
Bacteria Component in Emulsion *	24.8
Virus and Bacterial Components diluted 1/1000 in Emulsion	23.4
Saline in Emulsion	25.0
PAV	25 percent survivors

* - Peanut oil-arlacel-A aluminum monoesterate emulsion.

of 90 days. Vaccination with PAV resulted in fewer takes and in those animals where tumor take occurred the vaccination decreased the mortality.

Treatment with PAV protected from death 50 percent of the experimental mice, while all the untreated mice died, with an average day of death of 58 days. In this experiment not only did 50 percent of the animals receiving PAV survive, but the average day of death for vaccinated mice was 72.6 days.

In mice injected with Ehrlich's ascites tumor cells, the untreated group showed 89 percent mortality while the PAV treated group showed only 44 percent mortality. Preliminary results of experiments being conducted at the present time reveal that the intraperitoneal route is more effective than the intramuscular route in protecting mice from Ehrlich's tumor.

The growth of Ehrlich's tumor cells in Balb/c mice was followed using the weight of the animal as an indicator of the amount of ascitic fluid produced. The weight of the mice increased with the amount of ascitic fluid which increased with the amount of tumor cells. The animals in the group with tumor cells and no vaccine showed an increase in weight

until death of the animal; this group showed an average day of death of 20 days. In animals receiving tumor cells and treatment with PAV, the weight remains relatively constant during the duration of the treatment (4 weeks). After discontinuation of PAV treatment, 75 percent of the animals treated gained weight and died with an average day of death of 29.7 days, whereas 25 percent did not gain weight and were apparently free of disease for the duration of the experiment. The animals that only received PAV showed no significant change in weight nor any signs of toxicity. This group received 0.1 ml of PAV for 15 weeks without mortality.

When the tumor growth inhibiting capacity of PAV was compared to that of *Mycobacterium bovis* (BCG) in chondrosarcoma C₃H/Hej, mice model showed that the BCG filtrate alone protected 10 percent of the mice from death due to the tumor while PAV protected 50 percent of the mice. All the animals in the untreated group died during the experimental period of metastatic disease. This data demonstrates that in this model PAV is more effective than BCG. Protection by individual components showed that the virus component was the most effective of the individual components of PAV in pro-

protecting mice. The complete PAV was the most effective.

From the above experiments we may conclude:

1. A bacterial-virus-peanut oil arlacer-A-aluminum monostrate emulsion (PAV) is effective in protecting mice implanted with adenocarcinoma, chondrosarcoma and Ehrlich's ascites tumor cells. Note the generality of this effect in different tumors and different strains of mice.
2. PAV delayed colon adenocarcinoma growth in mice. Tumor growth is linear in vaccine-treated mice, while in the untreated ones the tumor growth is exponential.
3. The PAV decreased the tumor take and increased the survival time of tumor implanted mice.
4. The PAV is more effective than immunotherapy with *Mycobacterium bovis* strain BCG.
5. The growth of Ehrlich's ascites tumor cells is suppressed in mice treated with PAV. If vaccine treatment is discontinued tumor growth may recur. However, some animals are rendered free of tumor.
6. The viral component of the PAV is the

most active component, but is not as effective as the complete PAV.

Experiments on cytotoxicity (3, 4) and the histologic examination of the tissues showing infiltration of the dermis and peritumoral tissues by polymorphonuclear leukocytes (5) suggest a role for the macrophage. Preliminary experiments showed that the factor or factors involved in cytotoxicity and plating efficiency are inactivated at pH.2, are stable at 56°C and inhibit virus growth which suggest a role for immune interferon too.

It is evident from these data and from our other experiments that PAV has a definite effect on immunotherapy of experimental tumors. Several experiments are being conducted to identify the effect on the immune response. A controlled, randomized prospective clinical trial has been designed and approved and will start shortly.

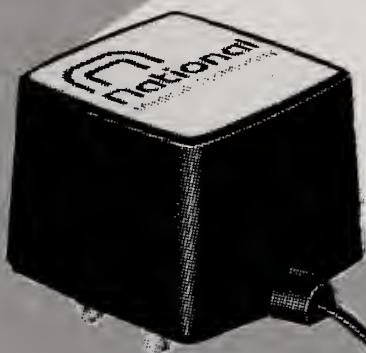
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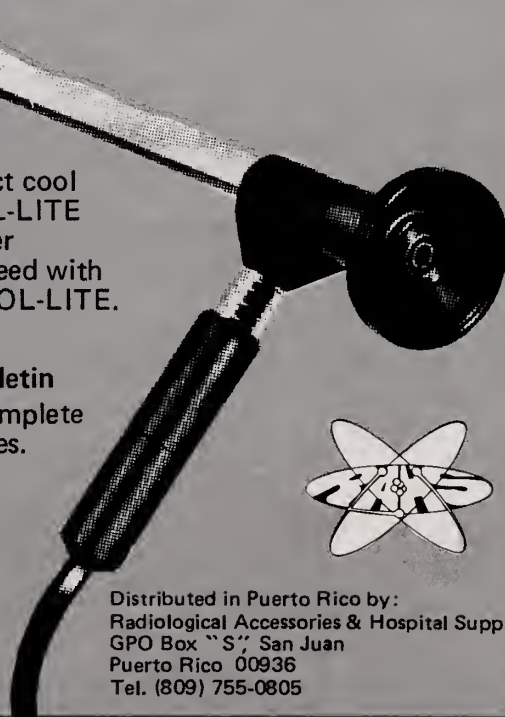
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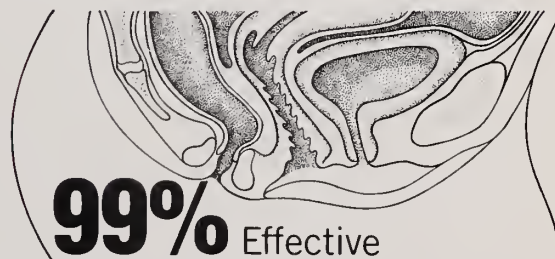
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In another study of 172 patients, many with recurrent cystitis, Septra achieved a 99.7% bacteriologic cure[‡] at end of therapy; 72.7% cure up to 18 days post-therapy.⁴

In the laboratory: Septra is effective against susceptible strains of *E. coli*, *Klebsiella-Enterobacter* and *Proteus*.[§]

PRESCRIBING CONSIDERATIONS: Septra is contraindicated during pregnancy and the nursing period, in patients hypersensitive to its components, and in infants under 2 months. During therapy maintain adequate fluid intake, perform frequent CBCs and urinalyses with microscopic examination.

*due to susceptible organisms

†tissue levels do not necessarily correspond to clinical effectiveness

‡10,000 or fewer organisms/ml urine

§*In vitro* data do not necessarily correlate with clinical results.

SEPTRA® DS

each tablet contains: 160 mg trimethoprim
and 800 mg sulfamethoxazole

The power to perform in recurrent infections of the upper and lower urinary tract.*

*due to susceptible organisms

SEPTRA® DS

Double Strength

Each tablet contains: 160 mg trimethoprim and 800 mg sulfamethoxazole

INDICATIONS AND USAGE:

URINARY TRACT INFECTIONS: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

NOTE: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of these urinary tract infections.

ACUTE OTITIS MEDIA: For the treatment of acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in the judgment of the physician, Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to *Haemophilus influenzae* resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: For the treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *Haemophilus influenzae* and *Streptococcus pneumoniae* when in the judgment of the physician, Septra offers some advantage over the use of a single antimicrobial agent.

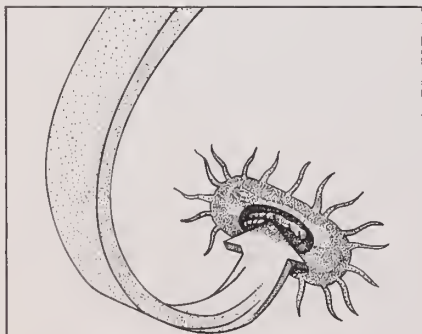
SHIGELLOSIS: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

PNEUMOCYSTIS CARINII PNEUMONITIS: Septra is also indicated in the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period (see "Reproduction Studies"). Infants less than two months of age.

WARNINGS: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A, β -hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.



Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but it has been reported to interfere with hematopoiesis in occasional patients. In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombopenia with purpura has been reported.

The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts should be done frequently in patients receiving Septra. If a significant reduction in the count of any formed blood element is noted, Septra should be discontinued.

PRECAUTIONS: Septra should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

It has been reported that Septra may prolong the prothrombin time of patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when Septra is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

ADVERSE REACTIONS: For completeness, all major reactions to sulfonamides and to trimethoprim are included below even though they may not have been reported with Septra.

Blood Dyscrasias: Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia.

Allergic Reactions: Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

Gastrointestinal Reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis.

C.N.S. Reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

Miscellaneous Reactions: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L.E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Goiter production, diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, ACUTE OTITIS MEDIA IN CHILDREN AND ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS.

Adults: The usual adult dosage for the treatment of urinary tract infections and acute exacerbations of chronic bronchitis is one Septra DS Tablet every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. In children weighing 88 lbs (40 kg) or more, the dosage is one Septra DS Tablet every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15-30	Half of the usual dosage regimen
Below 15	Use Not Recommended

PNEUMOCYSTIS CARINII PNEUMONITIS:

The recommended dosage for patients with documented *Pneumocystis carinii* pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. In children weighing 70 lbs (32 kg) or more, the dosage is one Septra DS Tablet every 6 hours for 14 days.

HOW SUPPLIED: Oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole — bottle of 100, unit dose pack of 100 and COMPLIANCE™ Pak of 20.

Also available in regular tablets containing 80 mg trimethoprim and 400 mg sulfamethoxazole (bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100) and oral suspension containing 40 mg trimethoprim and 200 mg sulfamethoxazole in each 5 ml (bottle of 473 ml. Unit of Use: bottle of 100 ml with child-resistant cap).

Reproduction Studies: In rats, doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palate. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In rabbits, trimethoprim administered by intubation from days 8 to 16 of pregnancy at dosages up to 500 mg/kg resulted in higher incidences of dead and resorbed fetuses, particularly at 500 mg/kg. However, there were no significant drug-related teratological effects.

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STUDIES ON THE MECHANISM OF BCG ACTIVATION FOR IMMUNOTHERAPY

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Mycobacterium bovis, strain BCG, and various products obtained from these cells have been used for immunotherapy of neoplastic diseases in animals and humans (1, 4, 6, 7, 11, 15, 16, 19-23, 29-31). This bacterium has been considered a non-specific immune stimulator, and although the mechanism of action is still unknown several observations suggest a more active participation of the live bacterium. Tumor regression induced by BCG has been found to be quite effective and more specific after contact with autologous tumor cells (12-14, 17, 27, 32-36). More indirect evidence comes from investigations by Seibert (26) who reported immunogenic activity (specifically delayed hypersensitivity reactions) in the culture media of the tubercle bacilli. Subsequently Seibert and Crowle (25, 5) observed that mycobacterial culture filtrates conferred protection in experimental animals against subsequent tubercular challenge. Hedgecock induced protection with mycobacterial culture filtrates against subsequent challenges with Klebsiella and Diplococcus pneumonia (10). These data suggested the presence of soluble immunopotentiating factors in the culture media.

With these observations in mind we have designed a series of experiments to answer the basic question: Will contact of Mycobacterium bo-

vis with tumor cells *in vitro* augment the anti-tumor effectivity of BCG? Will this be transmitted by the filtrate? Could this factor be a significant effector pathway in tumor immunotherapy?

Materials and Methods

Tumor Cells: Mouse sarcoma tumor cells, S180, were maintained as monolayers in Basal Medium Eagle (BME) supplemented with 10 percent calf serum and suspensions prepared to 10^6 cells/ml, and 0.2 ml of this suspension inoculated intraperitoneally in C3H mice. On the same day, 0.1 ml of the same suspension was added to the mycobacterial cultures.

Experimental Animals: Inbred healthy male and female C3H mice, were used. They were 12 to 15 weeks old and weighed 25 to 30 grams. The animals were housed five to a cage and provided water and Purina Laboratory Chow ad libitum.

Preparation of Columns: Sephadex columns G75-30 were prepared according to instructions. One ml of the respective filtrate was eluted with phosphate buffer solution pH 7.0. Fractions of 35 drops each were collected by an automatic Buchler Fractomette 200.

Preparation of Bacterial Cultures and Filtrates: Colonies from BCG 1029 (TMC) cultures on Lowenstein Jensen media were transferred to enriched Middlebrook 7H9 broth tubes. These were incubated at 36° and shaken daily. Growth was monitored every 2 days (1×10^7 bacterial cells/ml). One ml of stock culture was transferred to each of a series of tubes containing 9/ml of Middlebrook 7H9 broth. At this level of bacterial growth, 0.1 ml of S180 cells suspension (10^5 cells) was added to the culture. Aliquote portions of this

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TABLE I
Experimental Design

Mice Group	Tumor Cells S 180	BCG Culture Modifications	Treatment with Bacterial Product
Control I	1×10^5	-----	-----
Control II	1×10^5	1×10^4 /ml viable cells normal mouse kidney	Cell-free filtrate 0.2 ml Day +4 and +7
Control III	1×10^5	None	1×10^6 organisms of viable BCG Day +4
IV	1×10^5	None	Cell-free filtrate 0.2 ml Day +4 and +7
V	1×10^5	1×10^4 /ml viable Cells S 180	Cell-free filtrate 0.2 ml Day +4 and +7
VI	1×10^5	1×10^4 /ml viable Cells S 180	Sephadex fraction 2 of cell-free filtrate from BCG culture 24 hours after addition of S 180 cells. 0.2 ml Day +4 and +7
VII	1×10^5	1×10^4 /ml dead cells (boiled) S 180	Cell-free filtrate 0.2 ml Day +4 and +7

culture, after 4, 12, 18, 24 and 72 hours incubation (36°) were filtered through a Millipore filter 0.45 μ m. One ml of each filtrate was passed through the Sephadex column and the fractions read in a Gilford ultraviolet spectrophotometer at 260 nm.

Animal Experiments: Groups of ten animals each, five male and five females, were inoculated intraperitoneally with 0.2 ml of the indicated cell free preparation as shown in Table I. In general all animals had been inoculated intraperitoneally with tumor cells on day zero, in an amount of 10^5 tumor cells per mouse. Controls received no further treatment and were observed daily for tumor growth and survival. All other groups shown in Table I received cell-free filtrates on day +4 and +7 after tumor inoculation. The different groups reflect the incubation of mycobacterial organisms with either viable or dead sarcoma 180 cells, with viable kidney cells, or viable mycobacterial organisms alone, or with no tumor cells.

Results

Change in Growth Characteristics: These data will be reported elsewhere.

Effect on In Vivo Tumor Growth: Control animals injected 10^5 viable sarcoma 180 tumor cells which did not receive any treatment with either BCG or a cell-free filtrate were all dead by day 95. The average day of death was 64.5. Cell-free filtrate injected at day 4 and at day 7 improved survival to 20 percent. If the BCG culture was incubated with normal viable mouse kidney cells (10^4 /ml) survival was also increased to 20 percent. Viable organisms 1×10^6 injected intraperitoneally on day

TABLE II
Analysis of Survival

	PERCENT SURVIVAL	
	At Day 100	At Day 160
I (Tumor control) VS V (4 days Filtrate)	0 60	0 30
Significance *	$P < .01$	$.05 < P < .10$
I (Tumor control) VS VII (dead cells filtrate)	0 0	0 0
Significance *	NS	NS
V (4 day filtrate) VS VII (dead cells filtrate)	60 0	30 0
Significance *	$P < .01$	$.05 < P < .10$
II (NMK filtrate) VS IV (BCG filtrate)	20 20	20 20
Significance *	NS	NS
IV (BCG filtrate) VS V (4 day filtrate)	20 60	20 30
Significance *	$.05 < P < .10$	NS
III (microorganisms) VS VI (fraction 2) VS V (4 day filtrate)	40 30 60	30 30 30
Significance *	NS	NS

* Analysis by Fishers Test

+4 further increased survival to 30 percent. Survival of 30 percent was also observed when the initial BCG culture was incubated with viable S 180 tumor cells for four days and then a cell-free filtrate injected, also there was a 30 percent survival when

Sephdex Fraction 2 of the cell-free filtrate was injected on days 4 and 7. However, in this group 4 animals died very early (average 19.3 days). Fraction I corresponded to an albumin peak and was not injected. When the BCG culture was incubated with

dead tumor cells, no survivors were observed. Table II shows the statistical analysis of the results.

Discussion

Cell-free filtrates of BCG culture with live tumor cells improved survival of animals treated four and seven days after the initial tumor lead. This effect was the same as that of BCG organisms injected intraperitoneally and was abolished with treatment of BCG culture with dead tumor cells. The effect of only two injections is seen early in the survival curves, but is not so evident upon long term survival. Survivors, nevertheless remained free of disease. We are now studying the effect of multiple continuous injections of this product into tumor bearing mice to see if the survival can be improved.

The necessity of live tumor cells suggested either the elaboration of an auto-destructive factor by the tumor cell itself, or a response of the mycobacterium to a transfer of informational material from the tumor cells, and its defensive response to this material. The exact mechanism is not known but the fact that acquired immunity to tuberculosis is possible using only living BCG organisms suggests that these bacteria are more active than passive. Also, the fact that contact with tumor cells and direct inoculation into tumor in human experiments appears to give better results than when injected in sites distant to the tumor lesions, may argue in favor of this hypothesis. Mycobacteria are capable of producing natural products with widely divergent chemical structures and physiological properties (37). This appears to be a wide spread phenomenon in other organisms (38). Besides antibiotic (37) and toxic products (38), mitogenic factors have also been described (39).

Since we found that two injections of the induced soluble factor appear to be as effective in this model of immunotherapy as the viable complete mycobacterial organism, perhaps this soluble factor produced under controlled conditions could be used in place of the living mycobacterial vaccine. This

of course, could overcome some objections to the use of viable mycobacterium, such as risk of disseminated infection and other severe reactions that have been observed.

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IMMUNOLOGIC CONSEQUENCES OF SPLENECTOMY

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Splenectomy has been performed as a diagnostic or therapeutic maneuver in a variety of diseases. The relative technical ease and the low rate of immediate complications have made this a common surgical procedure. Until recently the only accepted treatment for traumatic splenic lacerations or rupture was splenectomy. Similarly, it has been considered a standard treatment for hematologic diseases such as hereditary spherocytosis and unresponsive idiopathic thrombocytopenic purpura. Furthermore, splenectomy has been utilized in the diagnosis and treatment of neoplastic conditions such as Hodgkin's disease, and as adjunct therapy in the field of organ transplantation.

It is becoming increasingly apparent that splenectomy carries with it certain long range consequences only recently identified. Historically, this field of investigation was ushered in by the clinical description of a significantly increased risk of overwhelming infections following splenectomy in children (1). At present there exists ample evidence that substantiates such predisposition in splenectomized patients (2, 3, 4, 5, 6). Paralleling this discovery, an expanding volume of work is attempting to define the specific effects of splenectomy on the immune system. As a result of these investigations, efforts have been made to prevent or compensate for these deleterious effects of splenectomy utilizing a variety of surgical and non-surgical methods.

Finally a new area, speculative at this time, forms the basis for new research dealing with the possible long term development of malignancy in the immunologically deficient post splenectomy patient. We would like to review the topic of the immunologic consequences of splenectomy under these headings of post splenectomy sepsis, specific defects in the immune system, attempts to compensate for post splenectomy immunologic deficiencies, and malignancy in the splenectomized patient.

Post splenectomy sepsis

King and Shumacker in 1952 called to our attention the syndrome of post splenectomy sepsis in children (1). He reported a 4 percent incidence of a clinical febrile syndrome of abrupt onset and rapid progression, characterized by a high mortality and caused by an exuberant growth of encapsulated gram positive bacteria in children with a previous splenectomy. Subsequent series have documented the occurrence of this highly lethal long term complication (2, 3, 4, 5, 6). The incidence has varied from 2 to 6 percent in these reports. In our own institution during the period of 1966-1977 we found a 2.6 percent incidence of overwhelming sepsis reported in children with splenectomy (7). The mortality rate once the syndrome is established has been variously estimated between 50-80 percent (2, 3, 4, 5, 6).

Several factors have been found important in determining this risk. Clinical series have noted a much higher incidence in infants and young children. It is estimated that as many as 40 percent un-

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dergoing splenectomy before the age of 4 years, will develop serious infection (8). Even though the risk decreases as the age increases, cases are being reported, with increasing frequency even in adults (9). The magnitude of the risk appears to be greater, the shorter the period from the time of splenectomy, and in particular during the first two years. However, even though the risk decreases with advancing time after splenectomy, an increasing number of cases are being reported of overwhelming sepsis long term after the initial surgical procedure (4, 5, 8, 10). It is becoming apparent that this may represent a life-long risk of serious infection for the splenectomized individual (10, 11). Another factor found important in defining the magnitude of this risk, is the specific indication for the splenectomy. Children with thalassemia major, histiocytosis and the Wiskott Aldrich Syndrome, who have major involvement of the reticulo-endothelial system, develop severe infection in approximately 20 percent (2, 6). In an intermediate group which includes the hematologic disorders of hereditary spherocytosis and hypoplastic anemia, the risk has been estimated at about 2 percent (2, 6). The risk following trauma is the lowest, but still estimated at 14 to 65 times greater than expected in the general population (10, 12). Some hypothesize that this particular group may be protected by the development in a significant proportion of patients of a functioning splenosis from inadvertent splenic implants (13).

Further underlining the importance of the spleen in the control of these serious infections are other studies showing an increased incidence of sepsis among children with congenital hyposplenism or asplenia (14, 15, 16), with functional asplenia as a result of sickle cell anemia (13), or following supradiaphragmatic splenic transposition for Chiari's disease (17).

Controlled experimental studies have documented and defined more clearly in animals the nature of this infectious propensity. With pneumococci as an intravenous challenge splenectomized rats have been shown to have significantly higher mor-

tality rates (18, 19). Similar responses have been found by other challenge routes, including aerosolized nasal spray, or intraperitoneal injection (8, 20). Partial protection has been demonstrated using several techniques short of total splenectomy, such as splenic artery ligation, partial splenectomy or peritoneal implants (2, 22), or by immunization (23, 24). Other approaches such as subcutaneous or muscle implantation or intraportal autotransplantation, while feasible have been shown to be less effective in protecting against pneumococemia (25, 26).

From the clinical and laboratory studies, one reaches the inevitable conclusion that the intact spleen plays an important role in the body defenses against overwhelming infections, that this function is dependent on multiple factors of age, length of time after splenectomy, amount and type of remaining splenic tissue, and other associated conditions.

Specific defects in the immune system

Once the risk of post splenectomy sepsis was well described and documented, research in this field took to the identification of the specific deficits assumed to occur in the immune system. This ongoing effort is at present incomplete. However, several experimental and clinical studies have begun to clarify this complex problem. Some researchers have shown that impaired clearance of blood-borne particles and bacteria follows splenectomy (18, 27). Others have demonstrated a decreased antibody response to specific antigens (21, 22, 28); altered levels of immunoglobulin (11, 29, 30), depression of T-cell responsiveness as measured by phytohemagglutinin stimulation (11, 25, 31), decrease in opsonization of bacteria and an absence of Tuftsin following splenectomy (32).

In our laboratories, we have been interested in characterizing the immunologic profile following splenectomy. We have tested a group of 25 children who underwent splenectomy for a variety of indications at our institution. Using the phytohemagglutinin lymphocyte stimulation test (P. H. A.),

migration inhibition factor (M. I. F.), serum immunoglobulin levels, and skin testing with antigens for mumps, streptokinase - streptodornase, candida and P. D. D., we are hoping to determine whether a specific pattern, measurable by these *in vivo* and *in vitro* test, develops after splenectomy. A second group of children is being tested sequentially, before and after splenectomy, in an attempt to characterize the temporal development of any defect in the immune system. To date, eight children with total splenectomy and five children with partial splenectomy have been entered into the study. On preliminary data, we have been unable to identify specific reproducible defects in the splenectomy group as a whole, but have noticed that some abnormalities (anergy), occurred more commonly in groups with a second underlying disease (e. g. Hodgkin's) or with other concomitant therapy (e. g. chemotherapy). Our present data base is too small to conclusively confirm the findings of some of the above mentioned groups. Our hypothesis is that as our experience becomes greater we may indeed be able to determine specific defects and their relation to the various contributing factors of age and underlying disease.

Attempts to compensate for post splenectomy immunologic deficiencies

In view of the already identified increased risk of developing overwhelming sepsis and of the specific immunologic deficiencies being reported, various strategies for dealing with this problem have emerged. In children where a total splenectomy has been performed or will eventually be necessary, the use of long term antibiotics, vaccination, or delayed splenectomy have been applied. Suppressive antibiotic therapy has been suggested for the period of highest risk following splenectomy, on a continuous or intermittent basis (16, 33). Draw backs to this includes the inability to adequately cover all the possible etiologic bacterial agents, emergence of resistance, and the side effects of this long term antibiotic therapy. Vaccinations against the most common causative organism is presently practiced. The pneumococcal vaccine (pneumovax) has been shown to

give good protection against the 14 most prevalent types of pneumococci, responsible for 80 percent of the pneumococcal infections (23, 24). Apparently effective vaccines against hemophilus influenza and Neisseria meningitidis are presently being tested (24). However, these vaccines do not cover all the potential bacterial agents, and may be less effective in splenectomized children than in those vaccinated with a normal functioning spleen.

The conservative treatment of splenic diseases has been applied in an effort to save the spleen and its function. Non operative treatment of splenic injury was advocated as early as 1971 by Douglas and coworkers (34). Other reports have confirmed that a high percentage of children with carefully diagnosed splenic injuries can be treated in a conservative nonoperative fashion, with significant complications (12). We reported our own experience in 20 children with splenic rupture with good results and definite evidence of splenic healing (35, 36). However, if bleeding is persistent an operative approach is required. In this case, several groups have shown that a splenectomy is not always needed and that repair of splenic lacerations or partial splenectomies may be performed without serious complications (10, 37). Our own limited experience with 5 patients confirms the safety of this approach. Experimental studies have supported the idea that there is a measurable immunologic advantage of hyposplenism (partial splenectomy, splenic artery ligation, autotransplantation) over total asplenism (21, 38).

Another situation where conservation of the spleen may be important is in staging procedures for Hodgkin's disease. The risk of post splenectomy sepsis in this group is particularly high. Chilcote reports 10 percent sepsis and 50 percent mortality in the Children's Cancer Study Group (39), while Ertel described a 25 percent sepsis and 33 percent mortality rates in a smaller group of children (40). We reviewed the staging laparotomies in children with Hodgkin's disease at the University Hospital for the years 1966-77 and found a 72 percent incidence of negative laparotomy, 22 percent splenic involvement only and 6 percent spleen liver and nodal involvement (7). We similarly reviewed tho-

se cases of splenic involvement and found a diffuse distribution of the lesions in 90 percent, and a focal distribution in only 10 percent (7). Based on these findings and confirmatory findings by other groups (41, 42), we have performed partial splenectomies in staging laparotomies for Hodgkin's disease in three children (7). All of these children had no involvement of the spleen on frozen or permanent sections of the specimen. We feel that the protection value of a partial splenectomy versus total splenectomy in this high risk group of children will be born out as further data accumulates.

Malignancy in the splenectomized patient

All the previously mentioned studies have suggested that splenectomized patient can be considered to be relatively immunologically deficient. From other studies it is well established that there is an increased risk for cancer in individuals with primary or acquired immunologic deficiencies (43). It is postulated that there is an "immunologic surveillance system" that acts to prevent in development of spontaneously - appearing malignant cells into established tumors. We have been interested in the possible long term effects of splenectomy in the development of malignancy. There is a dearth of information concerning this question in the literature. Robinette studied a group of soldiers who underwent splenectomy during World War II and reported no increased incidence of cancer in this group of young men as compared to matched controls (44). However, this particular population studies had splenectomy at an age well beyond childhood. If we postulate that the risk of long term development of cancer parallels the risk of overwhelming sepsis, one would have to postulate that only when we study groups of children, who underwent splenectomy, might we be able to find the differences in the long term development of cancer. At present we hope to begin such a study in children who underwent splenectomy 20 to 30 years ago, and compare the incidence of development of cancer in these groups with other control groups. This interesting field of inquiry however, remains only a speculative one.

Conclusions

Splenectomy can no longer be considered an innocuous procedure in spite of its relative technical ease and its low incidence of immediate complications. There is a well described and amply documented increased risk of overwhelming sepsis following splenectomy. Progress has been made in identifying the specific defects in the immunologic system that follows splenectomy and in attempting to correlate these changes with the various factors known to be important in the development of these significant infections. Important technical approaches for conservative treatment of the spleen, and other preventive alternatives for the already splenectomized patient, have been defined and are being successfully used. Finally, although in a speculative phase, the important question of the relation of splenectomy and the development of malignancy is actively being investigated. It is hoped that these multiple investigative approaches of the long term problems of splenectomy may place this procedure in its proper perspective, and give us further insight into the immunologic functions of the spleen.

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IMMUNOLOGICAL ASPECTS OF PERIODONTAL DISEASE

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Periodontal disease (PD) or "Pyorrhea" is the principal cause of tooth loss in adults and affects more than 40 percent of the population. Clinically it is divided into gingivitis and periodontitis. The symptoms include bleeding of the marginal gingival tissues, tooth mobility and tooth migration. The disease follows a painless, chronic course with alternating periods of quiescence and exacerbation. The complex mass of bacteria that organize, multiply and mature on the tooth surface is termed dental plaque (dp) and it is the etiological factor in this disease (1).

The relative proportion of different groups of organisms in the mixed flora of dp have been correlated with different levels of tissue destruction. Among these, the gram negative anaerobic organisms are associated with the most advanced stages of the disease.

The gingival tooth interface (junctional epithelium), is the initial area of breakdown where an acute inflammatory response is established in the underlying connective tissue. Eventually a state of chronic inflammation is established which is characterized histopathologically by proliferation, apical migration and lateral extension of the junctional epithelium, a presence of lymphocytes, macrophages and plasma cells, a continuing loss of connective tissue substance coupled with fibrosis at more distant sites, extension of the inflammatory component into the alveolar bone and periodontal ligament, and osteoclastic bone resorption sometimes ahead of the inflammatory component (2).

An important consideration in the disease process is that the microorganisms never invade the tissues; that is, no infection occurs. Rather, the continued immunological stimulation induces the tissue damage observed (3).

A lymphoblastic response to dental plaque by peripheral blood lymphocytes has been shown to occur in vitro and to be related to the level of clinical PD (4). Also, cord blood lymphocytes, from mothers with PD have been shown to transform in response to dp to the degree of maternal PD (5).

The bacterial enzymes from dp are believed to make the epithelial barrier permeable to bacterial antigens. These antigenic bombardments initially attack polymorphonuclear leukocytes and subsequently induce a lymphoblastic response. Macrophages migrate into the area and lymphocytes become the predominant cell during the early stages. As the lesion advances, plasma cells become more numerous and in the later stages predominate. An inverse relationship between the numbers of lymphocytes and plasma cells has been reported (6). Most plasma cells contain Ig G, some contain Ig A while Ig M and Ig E are rare (7). Immunoglobulin in the inflamed tissue has been shown to be specific against oral bacteria (8), and antigen-antibody complexes (9) as well as products of activated complement (10) have been demonstrated. C 5 related compounds have been implicated as being primarily responsible for the mononuclear cell chemotaxis (11). Macrophages and mast cells are sources of prostaglandins (PG) in this area. PGE has been shown to be highly increased in this area and it is believed to play a role in the pathogenetic process (6). Localization of PGE to within and beneath the inflamed epithelium as well as in the endothelial cells of small vessels and leukocytes has been shown (6). Mast cells

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are found in normal tissue and their number has been shown to decrease with increasing level of inflammation (12). The release from mast cells of histamine, heparin, proteolytic enzymes and anticollagenase inhibitor as well as PG is believed to play an stimulatory role. The release of PGE from macrophages may play an inhibitory role as well as a stimulatory one. The increased release of PGE may suppress lymphocyte activation, secretion of lymphokines and suppress antibody dependent cellular cytotoxicity.

Bacterial lipopolysaccharide (13) (LPS) (endotoxin) has been shown to be present in the gingival sulcus in direct relationship with the amount of both clinical and histological inflammation. LPS can stimulate macrophage production of PG, cyclic AMP and collagenase. LPS is also a well known B-lymphocyte mitogen and could account for the observed shift from a lymphocyte lesion into a plasma cell lesion.

The most important factor of the disease process as it relates to tooth mortality is loss of alveolar bone (14). Osteoclastic bone resorption, sometimes ahead of the cellular infiltrate, is a characteristic of the disease. In vitro assays have shown that both LPS and PGE can mediate bone resorption. Alternatively, a lymphokine osteoclast activating factor (OAF) produced by activated lymphocytes in culture has been shown to induce osteoclastic bone resorption (15).

Dental Plaque can activate complement through both the classical and the alternative pathways and can generate a C 3- cleaving enzyme activity (16).

Studies on the role of secretory Ig A have not been conclusive. It is accepted that secretory Ig A coats the bacterial surfaces and the oral structures, influencing in this manner the adhesion of bacteria, which is the first step in dp formation. However, other studies suggest that secretory Ig A may enhance interbacterial adhesion.

It is obvious that PD is a multifactorial disease and that bacterial host interactions are of tremendous importance. Other factors, seemingly independent of the immune response, have also been shown to influence the course of the disease process. The level of home oral hygiene as it influences dp and the forces generated on the teeth as a result of

hyperfunction (occlusal traumatism) are two of these factors. Further understanding of the immune aspects of the disease will hopefully lead us to cure or prevent it. Unfortunately, apart from fastidious home oral hygiene measures and surgical debridement of the areas, no other means of treatment for the disease is yet available.

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ADVANCEMENTS IN HYPERSENSITIVITY DISEASES

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The field of hypersensitivity diseases is one of the youngest in the history of medicine. It had its beginning during the early part of this century when Prusnit and Kustner tested a patient who had fish sensitivity, with fish extract, developing a positive skin test. Following this, they transferred the patient's serum to a normal person and tested him with fish extract and the normal person developed a positive skin test. This is known as the P-K Reaction. These investigators called this serum factor, capable of transferring specific sensitivity, a "reagin".

This finding lead to study the model of experimental anaphylaxis in the guinea pig to understand the nature of the reagin by comparing human reagin with that of the guinea pig. It has shown that the reagin had long periods of sensitization and that it persisted. The maximal titers of reagin antibodies as obtained by the P-K Reaction are obtained when the sensitized site is challenged 24-48 hours after the passive transfer. When the interval between the sensitization period and the challenge was 3-4 hours, you have to use a ten-fold concentration of the reaginic antibodies to obtain a positive skin test. The local sensitization with reagin persisted for 2 or more days. This property is different from the guinea pig gamma-1.

Although there was evidence of the existence of the reagin, it could not be characterized. In the early 1960's it was thought that the reaginic antibodies belonged to the IgA class of immunoglobulins, but it was shown that this was not sustained by the evidence on hand. It was in 1966 that Ishizaha and Johansson, independently, demonstrated

that the reagin activity resided in a new class of antibody called IgE, and was characterized it. IgE has a molecular weight of 197,000 and is made up of 2 heavy chains with a molecular weight of 72,300. These heavy chains are known as Epsilon chains; in addition there are 2 light chains, these are denominated as kappa and lambda chains.

IgE has a serum concentration varying between 0 - 0.002 ng/ml., a half-life of 2 days, does not cross the placenta, does not activate the classic complement cascade, is capable of activating the alternate complement pathway, and most significantly, binds to basophiles and mast cells. IgE has an optimal latent period for maximal sensitization of 1-3 days, which persists for 2-3 weeks. It is inactivated by heat (56 C for 2-4 hrs.) or by reduction alkylation treatment.

The identification of the antigenic determinants of the IgE molecule was possible following the fragmentation of the molecule after the digestion with either papain or pepsin. After the pepsin digestion, the resultant fragments are designated as Fab₂ and Fc. The resultant fragments following papain digestion are designated as Fab (there are 2 of these) and Fc.

The Fc fragment contains determinant of at least 2 different specificities E₁, E₂ one of the determinant E₁ is shared by Fc₁. The Fd portion is composed of a heavy chain that contains the idiotypic antigenic determinant E₀. Fab₂ shares E₁ antigenic determinant with Fc. Fc₁ fragment corresponds to the amino terminal third of the Fc portion of the heavy chain. The epsilon chain have 5 domain, 2 in the Fd portion and 3 in the Fc portion.

IgE most important property is its ability to bind to basophils and mast cells. It combines with the target cell through the Fc fragment. Heating or reduction alkylation treatment causes loss of the

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affinity by causing conformational changes in the Fc fragment. The average number of cell bound IgE molecules varies between 10,000 and 40,000 per basophil in most cases studied and was of the same order of magnitude in atopic and non-atopic individuals. The number of cell bound IgE does not necessarily parallel the concentration of IgE in the serum. The binding of IgE with its receptors seem to be a reversible process. IgE has a high affinity and low dissociation constant (1.3×10^9 M) which explains why it is so persistent.

In order to cause mediator release, there is bridging of 2 IgE molecules in the target cells. Assuming that IgE antibody is 5-10 percent of the total IgE, one can expect that the number of IgE antibody molecules on the cell surface would be 500-5,000.

It is difficult to expect that adjacent IgE molecules are antibodies of the same specificity. However, recent knowledge of the structure of the cell membrane suggests that the membrane is in a liquid state and surface immunoglobulins are movable at 37 C. One can visualize the allergen bound with a single IgE molecule. Moving around the cell surface and subsequently combining with another cell bound antibody molecule. The bridging phenomenon activates an enzymatic reaction which causes the release of the mediators: histamine, slow-reacting substance of anaphylaxis (SRA), eosinophile chemotactic factor of anaphylaxis, which are responsible for the clinical manifestations of the disease.

After having characterized and understanding how IgE mediates allergic disease, the next big step was to measure specific IgE *in vitro*. This was accomplished by using the RAST method. This is a 2 step procedure which is similar in principle to the indirect Coomb's test. In the first step the allergen is covalently bound to a solid phase supporting polysaccharide, such as cellulose particle or filter paper, and then it is reacted with serum. IgE antibodies as well as antibodies of the other immunoglobulins (particularly IgG) react with the solid phase allergen and form antibody complexes. IgE antibody directed against allergens other than those on the solid phase support, as well as other serum components are washed away at the end of the first step of the

reaction. In the second step of RAST, solid phase allergen-antibody complexes are reacted with radiolabeled (affinity chromatography purified) antibody to IgE. After another washing step to remove unbound anti-IgE, the radioactivity associated with the complex is measured in the scintillation counter. The quantity of IgE is proportional to the radioactivity measured. RAST results can be expressed in terms of total radioactivity counts bound, percent of binding produced by non-allergic serum standard, or arbitrary units or score based on comparison to the binding produced by a high titered positive serum.

Results of RAST have been shown to correlate with bronchial and rhino-conjunctival challenge procedures, for a variety of allergens. In addition, there is a fair agreement between RAST and symptom scores indices and end-point test titration, in patients sensitive to ragweed and hay fever patients.

RAST offers some advantages over skin testing in the diagnosis of allergy:

1. There is no patient risk
2. Results are quantitative
3. It is convenient to the patient
4. Results not influenced by drugs
5. Allergens are stable in the solid phase

RAST is preferable to skin tests in the following patient groups:

1. Infants
2. Patients with dermatographism
3. Patients with widespread dermatitis

There is a good correlation with clinical severity of the disease and histamine release studies.

Among the disadvantages of RAST are:

1. Expense in setting-up the procedure
2. Lack of widespread availability of radiolabelled anti-IgE.
3. Relatively lower sensitivity of RAST as compared to skin test.

In addition to the diagnostic measurement

of serum IgE antibodies to various allergens. RAST has also been utilized to measure the potency of allergy extracts.

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New evidence is in: Treatment of mild hypertension can save lives

Even among patients with DBP in the low 90s, systematic therapy significantly reduced mortality:

- Of nearly 11,000 hypertensives identified by the Hypertension Detection and Follow-up Program, slightly more than 70% had mild hypertension (DBP 90-104 mm. Hg).¹
- Half were given systematic and aggressive care in HDFP centers; half were referred to customary sources of medical care.
- After 5 years, HDFP found that effective treatment of mild hypertension may reduce premature deaths by 20%.¹
- As part of HDFP's systematic treatment and follow-up program, the primary step-1 agent was chlorthalidone: Hygroton.^{®2}

**The primary agent used by the HDFP
in an effective low dose**

Hygroton[®] 25 mg.
(chlorthalidone USP) **one a day**

**Because there's nothing mild
about mild hypertension**

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and

related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg (white, scored), 50 mg (aqua) in bottles of 100, 1000 and 5000; 25 mg (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References

1. Five-year Findings of the Hypertension Detection and Follow-up Program: 1. Reduction in Mortality of Persons With High Blood Pressure, Including Mild Hypertension, JAMA 242: 2562, Dec. 7, 1979. 2. Payne, G.H. Presentation of HDFP findings (Nov. 27, 1979), data on file, USV Laboratories.

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Manati, P.R. 00701

Fragile



handle with **HALDOL**[®] (haloperidol) tablets/concentrate/injection

controls disturbed behavior usually without complicating side effects

HALDOL haloperidol effectively controls psychotic symptoms, including disruptive behavior, without undue sedation—permitting a better quality of life for many disturbed elderly patients.¹ While some instances of drowsiness have been reported, marked sedation is rare.

Minimizes likelihood of cardiovascular complications

HALDOL is unlikely to cause hypotension which can result in dizziness and falls.² Transient hypotension seldom occurs; severe orthostatic hypotension has not been reported.

Few troublesome side effects

Blurred vision, dry mouth, constipation and urinary retention—which can be extremely upsetting to older

persons suffering from dementia—are infrequent with HALDOL.³

Extrapyramidal symptoms, when seen, are generally dose-related and readily controllable; usually they do not occur at the very low doses of HALDOL used in treating the elderly.^{4,*}

Tasteless, odorless, colorless concentrate

HALDOL concentrate can be added to food, juices or water to improve acceptability in patients unwilling or unable to swallow solid medication. It also permits the very small dosage adjustments sometimes needed for geriatric patients.

* Persistent extrapyramidal symptoms may require discontinuation of the use of the drug.

Photograph posed by professional model

Please turn page for summary of prescribing information.



concentrate

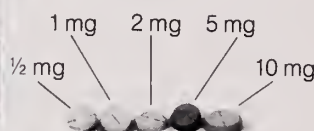
A tasteless, odorless, colorless liquid concentrate for better patient acceptability: 2 mg per ml haloperidol (as the lactate).

injection

A rapid-acting injection for psychiatric emergencies: 5 mg haloperidol (as the lactate) with 1.8 mg methylparaben and 0.2 mg propylparaben per ml, and lactic acid for pH adjustment to 3.4 ± 0.2 .

tablets

5 tablet strengths for convenience in individualizing dosage:



HALDOL® (haloperidol)

tablets/concentrate/injection

A dosage form for every therapeutic need

Summary of Prescribing Information

Contraindications: Severe, toxic CNS depression or comatose states from any cause, hypersensitivity to the drug, Parkinson's disease.

Warnings: Usage in Pregnancy: Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards. Infants should not be nursed during drug treatment.

Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity.

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticonvulsant medication since HALDOL haloperidol may lower the convulsive threshold; (3) with known allergies or a history of allergic reactions to drugs. Concomitant antiparkinson medication, if required, may have to be continued after HALDOL haloperidol is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time. The 1, 5, 10 mg tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Adverse Reactions: CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn.

Persistent Tardive Dyskinesia: Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by re-institution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms.

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice reported. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia and hypoglycemia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other neuroleptic drugs.

The injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

Caution: Federal law prohibits dispensing without prescription.

1892

IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

HALDOL tablets and concentrate (120 ml) are manufactured by McNeil Pharmaceutical Co., Dorado, PR 00646.

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References:

1. Smith GR, et al. *Psychosomatics* 15: 134, 1974. 2. Tobin JM, et al. *Geriatrics* 25(6): 119, 1970. 3. Bernstein JG: *Clinical Psychopharmacology*. Littleton, MA, PSG Publishing Company, 1978, p 23. 4. Slotky BA, in DiMascio A, and Shader RI: *Butyrophenones in Psychiatry*. New York, Raven Press, 1972, p 71.

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El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y la del impresor, se requiere de los autores que sigan las siguientes instrucciones:

Manuscrito: El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos a maquina a doble espacio y por un solo lado de cada página, en **TRIPLICADO** y con amplio margen. En página separada deberá incluirse lo siguiente: título, nombre del autor(es) y su grado (ej: MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse como un encabezamiento al centro y en letras mayúsculas.

Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

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Nomenclatura: Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

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In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

Manuscripts: The entire manuscript, including legends and references should be typewritten double spaced in **TRIPLICATE** with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgment of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscript should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by center headings in capital letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Material and Methods, Results if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

Nomenclature: Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurements should be used preferentially.

Tables: These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical and horizontal lines

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Wintrobe MM: *Clinical Hematology*, 3rd Ed Lea and Febiger, Philadelphia 1952 p 67.

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Health and Safety Tip

From the American Medical Association

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Alcoholism Strikes Millions In Nation

Alcoholics Numerous

There is no accurate count of the number of alcoholics in the United States. Estimates range from 10 to 12 million.

Although it is not known with certainty whether the incidence of alcoholism is increasing or decreasing, most indicators show that it is rising.

A pamphlet from the American Medical Association points out that an estimated 10 million people have a significant and recent alcohol-related problem and that another 10 million have experienced some type of alcohol-related problem during their lifetime. Close to one million people are receiving help for alcoholism at the present time.

Alcoholism seems greater in large cities than in smaller towns and rural communities, but differences are not great. Although alcoholism is more prevalent among men than women, an increasing number of studies show that because female alcoholics tend to be more shielded, the actual difference between the sexes may

be much smaller than commonly believed. The number of known women alcoholics has doubled since World War II.

No one can doubt the serious medical, social and economic consequences of alcoholism. The cost to the nation has been estimated to be \$25 billion a year due to absenteeism, health and welfare services, property damage and medical expenses.

Alcohol is a factor in about half of the automobile crashes in which there was a death, and is a serious factor among adult pedestrians who are killed. Major industrial firms have established that the alcoholic employee is absent from work more days per year than the nonalcoholic, and can expect to die sooner.

Alcoholics can be treated, but their illness is on-going or chronic. Control short of cure is acceptable. Although total abstinence is a desirable aim, improvements in social or occupational adjustments may be far better guides in determining whether a treatment effort is succeeding.

The alcoholic who suffers a temporary relapse during treatment is no more a failure than the diabetic who occasionally strays from his diet. The primary goal of treatment is to help the alcoholic discover more effective ways than drinking to deal with the stresses of living.



March, 1981
Frank Chappell
Science News Editor
AMA

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- improvement reported in 75% of 4,757 patients†1

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- steady decline in mean number of inflamed joints³
- symptomatic control maintained over three years of therapy³

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Convenient starting dose: usually 1 capsule t.i.d. with meals.

May be safely administered with other needed therapies: does not interfere with concomitant hypoglycemic¹ or anticoagulant⁴ medication.

¹For patients classified as Functional Class IV (incapacitated with little or no self-care), safety and effectiveness have not yet been established.

†Includes patients with minimal, moderate, and marked response to therapy.

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TOLECTIN® DS (tolmetin sodium)

double-strength capsules—for oral administration
Description: TOLECTIN DS (tolmetin sodium) capsules contain tolmetin sodium as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium.

Contraindications: *Tolmetin* (tolmetin sodium) should not be used in patients who have previously exhibited intolerance to it or patients in whom aspirin and other non-steroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria.

Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported.

If *Tolmetin* must be given to patients with active peptic ulcer, closely supervise the patients for signs of ulcer perforation or severe gastrointestinal bleeding.

Precautions: *General*—Clinical studies of up to two years duration have shown no changes in the eyes attributable to *Tolmetin* (tolmetin sodium) administration; however, because of ocular changes observed clinically with other non-steroidal anti-inflammatory drugs, ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.

There has been no evidence of renal toxicity to date in clinical studies, however, since *Tolmetin* is eliminated primarily by the kidneys, closely monitor patients with impaired renal function; they may require lower doses.

Tolmetin prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when *Tolmetin* is administered.

In patients receiving concomitant *Tolmetin*-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

Tolmetin should be used with caution in patients with compromised cardiac function.

The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g. sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips (e.g. Albustix®, Uristix®, etc.).

Usage in Pregnancy—Since *Tolmetin* has not been studied in pregnant women, the use of *Tolmetin* during pregnancy is not recommended.

Nursing Mothers—Because *Tolmetin* may be secreted in human milk, as a general rule nursing should not be undertaken while a patient is on this drug.

Drug Interactions—Although *Tolmetin* has been found *in vitro* to bind extensively to plasma protein, it does not alter the dosage of warfarin required to maintain a uniform prothrombin time.

In adult diabetic patients under treatment with either sulfonylureas or insulin, there is no change in the clinical effects of either *Tolmetin* or the hypoglycemic agents.

Adverse Reactions: *Gastrointestinal System*—The most frequent adverse reactions which occurred were gastrointestinal: nausea, 1 in 9 patients; dyspepsia, 1 in 10 patients; abdominal pain, 1 in 15; gastrointestinal distress, 1 in 15; flatulence, 1 in 25; diarrhea, 1 in 25; constipation, 1 in 40; vomiting, 1 in 30; gastritis, 1 in 55; and significant gastrointestinal bleeding without evidence of peptic ulceration, 1 in 240.

The incidence of peptic ulcer in about 3000 patients treated up to two years in clinical studies was about 1 in 50. Thirty-four percent of the ulcer patients had prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs, including corticosteroids, known to produce peptic ulceration.

In clinical trials about 10% of patients dropped out because of adverse reactions, mostly gastrointestinal in nature.

Body as a Whole—headache, about 1 in 10 patients; asthenia and chest pain, less frequently; and, rarely, anaphylactoid reactions.

Cardiovascular—edema, about 1 in 15 patients; hypertension, less frequently.

Central Nervous System/Psychiatric—dizziness or lightheadedness, about 1 in 20 patients; tension or nervousness, 1 in 50 patients; drowsiness, 1 in 60 patients; insomnia and depression, less frequently.

Dermatologic—rash, about 1 in 40 patients; pruritus, 1 in 60 patients; skin irritation, 1 in 55 patients.

Special Senses—tinnitus, about 1 in 65 patients.

Hematologic—Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred. This is similar to that reported with other non-steroidal anti-inflammatory drugs. A few cases of granulocytopenia have been observed.

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For information on symptoms and treatment of overdosage, see full prescribing information.

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References: 1 Data on file, Medical Division, McNeil Pharmaceutical. 2 Reid RT, Levin J, Ricca LR, et al: Tolmetin sodium in the treatment of chronic osteoarthritis: an analysis of 725 patients with a year or more of therapy. *Curr Ther Res* 28:173-184, August 1980. 3 From a three-year, multi-clinic open evaluation of *Tolmetin* tolmetin sodium, involving 42 patients with rheumatoid arthritis. 4 Whitsett TL, Barry JP, Czerwinski AW, et al: Tolmetin and warfarin: A clinical investigation to determine if interaction exists, in Ward JR (ed) *Tolmetin, A New Non-Steroidal Anti-Inflammatory Agent. A Symposium*, Washington, DC, April 1975. Princeton, Excerpta Medica, 1976, pp 134-141.

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Tylenol w/Codeine

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Atarax
Minizide

ROCHE LAB.
Bactrim
Librax
Valium

SMITH, KLINE & FRENCH
Dyazide

THE UPJOHN COMPANY
Motrin

U.S.V. LAB.
Hygroton

IMMUNOLOGIC ASPECTS OF LEPROSY

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Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*. As other chronic infectious diseases, which are associated with impaired cell immunity, the recent advances in immunology have made leprosy a comprehensible entity.

The significance of the altered immunologic reactivity in leprosy, together with the value of immunology in the diagnosis and treatment of the disease are discussed in this paper.

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. It presents a variable clinicopathologic spectrum which is determined by the host response to the infection. Although it was one of the earliest human diseases associated with an infectious agent, the recent advances in immunology have made leprosy a comprehensible entity. Many aberrations of the immune system have been described in this condition.

For a rational understanding of the disease and for any immunological investigation, the polar concept of its clinical expression is fundamental (1). Tuberculoid and Lepromatous forms are the poles of the disease. Tuberculoid leprosy is characterized by high resistance, few clinical lesions and a histologic appearance of delayed hypersensitivity with very few lepra bacilli. Lepromatous leprosy is characterized by generalized disease with foamy macrophages loaded with bacilli; i. e. low resistance. Between these

poles, there is an indeterminate number of presentations with various admixtures of tuberculoid and lepromatous components.

Ridley and Jopling (2, 3) propelled a classification that retained the polar concept (tuberculoid TT, and Lepromatous - LL) with a borderline group (BB) and adding two intermediate categories: borderline with tuberculoid features (BT) and borderline with lepromatous features (BL). Other unstable groups have been added close to the poles (Indeterminate tuberculoid and Indeterminate lepromatous).

Anergy (loss of allergic response) is consistently observed in persons with lepromatous leprosy which fail to manifest delayed-type hypersensitivity to intradermal challenge with antigens of *mycobacterium leprae* (4). In addition, many of those with lepromatous leprosy fail to react to skin test with "recall" antigens. The significance of this altered immunologic reactivity will be discussed in this paper.

Lepromin Test

The lepromin test (5) consists of the intradermal inoculation of a small quantity of biologically standardized extract of lepromatous tissue.

The early (Fernández) reaction, read at 48 hours, has the histologic characteristics of a tuberculin reaction and has been irregularly conferred on LL patients with previously negative reactions with whole lymphocytes or transfer factor (6). The late (Miranda) reaction is a kind of delayed hypersensitivity which attains its maximum by the 21st. day. It is completely negative in the presence of lepromatous leprosy and variably positive in tuberculoid and borderline le-

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prosy, being highly positive in major tuberculoid leprosy. It has not been reproducibly passively transferred with whole lymphocytes or transfer factor (7, 8). Although it reflects the immunologic reactivity of the patient, it has no diagnostic value.

An understanding of lepromin unresponsiveness, the most widely reported abnormality characterizing BB to LL patients, is fundamental in the understanding of the pathogenesis of the disease.

Humoral Immunity

Hypergammaglobulinemia seems to occur commonly in patients with lepromatous leprosy (9, 10, 11). Production of antibodies to unrelated standard antigens appears to be normal in both poles forms of the disease. Antimycobacterial antibodies are found in the majority of lepromatous and a minority of tuberculoid patients (11). IgM has been identified by immunofluorescence at the dermo-epidermal junction of involved and uninvolved skin in lepromatous leprosy (12). The significance of this humoral response is unknown but the defect may result from the presence of suppressor cells, which have been described in other chronic infectious diseases, which are associated with impaired cell mediated immunity (13).

Circulating immune complexes have also been described in leprosy (14), but their true role seems to be in the pathogenesis of leprosy reactions, namely Erythema Nodosum Leprosum and Lucio Phenomenon. We have been able to identify such complexes by the C_{1q} assay in five patients with Erythema Nodosum Leprosum. These patients also presented deposition of complement and immunoglobulins on the wall of the vessels of the upper dermis (15). The antigen and the role of immune complexes are unknown at the present moment.

Cell-Mediated Immunity

Cellular immunity provides the important

mechanism of defense against leprosy infection, preventing the establishment of the bacilli in the tissue, or preventing the appearance of overt lesions, or limiting the infection. Generalized impairment of cell-mediated immune responses, i. e. responses to antigens other than those of *M. Leprae*, has been reported in lepromatous patients (BL to LL) (4). The lymphocytes of lepromatous patients are non reactive to *M. Leprae* even when such cells are obtained from patients who have received long-standing chemotherapy. Other deficient parameters in lepromatous leprosy are intradermal skin tests (16, 18), epicutaneous allergic sensitization to a hapten (16, 17), allograft rejection (19), antigen-induced lymphocytes transformation and measurement of peripheral blood T-lymphocytes and lymphokine production in vitro (20). This deficiency is independent of the lepromin reaction since the latter remain negative in spite of adequate chemotherapy, while not the delayed hypersensitivity parameters.

However, it is very interesting that the "nude" mouse, a genetically T-cell deficient animal, does not develop a systemic infection after inoculation with *M. Leprae* (21). Studies in mice chronically infected with mycobacteria organisms do indicate that the equilibrium is shifted toward a dominance of suppressor-cell activity such that the net algebraic sum of helper and suppressor function is expressed as hyporesponsiveness (22).

A disease resembling lepromatous leprosy has been produced in mice in which cell-mediated immunity has been suppressed by neonatal thymectomy and irradiation (22). If the mice are first transplanted with lymphoid tissue from animals with normal cellular immune state, just after thymectomy and irradiation, and are then inoculated with mycobacterium leprae, the resulting infection is much less severe.

The capacity of other inflammatory cells such as the macrophage to participate in the development of cell-mediated immunity most likely represents a major instrument of ultimate destruction of *M. Leprae*. Most studies indicate that phagocytosis and lysis of *M. Leprae* are impaired in lepromatous leprosy probably resulting from a defective arming of the macrophages by T-lymphocytes sensitized to the antigen (23).

TABLE I
Immunity in Leprosy

	Lepromin positive	Delayed Hypersensitivity	Increased Immunoglobulins	Organisms
Tuberculoid Polar (TT) High resistance form	Usually positive	Usually normal	Yes	1 per 100 o.e.f *
Borderline Tuberculoid	Variable	Variable	Yes	1 per 10 o.e.f.
Borderline	Negative	Variable	Yes	1-10 per o.e.f
Borderline Lepromatous	Negative	Impaired	Yes	10-100 per o.e.f.
Lepromatous Polar (LL) Low resistance form	Negative	Impaired	Yes (higher)	10-1,000 per o.e.f.

* - Oil Emersion Field

Cellular immunity has not been as extensively studied in tuberculoid patients. If present, the immunologic impairment is of less severity than in lepromatous patients. In others, no generalized impairment has been identified.

Genetics

Genetic factors determining resistance or susceptibility to leprosy infection have long been suspected, and recent experience showing concordance rates of 80 percent in monozygotic twins (for leprosy, and for the type of leprosy) are very suggestive (24). Investigation of genetic markers, however, has given equivocal results. The notion of a genetic defect in lepromatous type is supported by the recent observation of increased frequency of two HLA specificities in those with this type (25).

Immunotherapy

Considerable effort has been spent in attempts to correct the presumed deficiency of the cell-mediated immune response in lepromatous patients

by administration of transfer factor (7, 8), the massive transfusion of allogeneic leukocytes (26) or by repetitive vaccinations with the bacillus Calmette-Guerin (27, 28). Although none of these therapies has been established as successful, the intravenous infusions of leukocytes from normal donors must be further studied. In our Service, preliminary results of a patient with lepromatous leprosy treated by this method, show definite improvement at the clinical, histological and immunological level as compared to standard chemotherapy (29). New patients are being carefully included and treated in this way.

The value of BCG vaccination as a prophylactic vaccine against leprosy is still in dispute, the evidence from trials in Uganda, Burma and Papua New Guinea being equivocal (27, 28). To date, the incidence of leprosy is similar in vaccinated individuals and in controls.

Greatly increased supplies of *M. Leprae* from infected armadillos and improved methods for purifying bacilli free from armadillo tissue have led to the hope that pilot vaccine field trials can soon be conducted (30).

In the meanwhile, chemotherapy, based mainly on the use of sulfones is still the treatment of choice of the leprosy patient. Patients with lepromatous

leprosy usually require therapy for the rest of their lives.

Conclusion

Since many investigations are still proceeding, it is not yet possible to make definite statements as to the future of leprosy. Many theoretical questions still remain unanswered, but studies like those on the efficacy of immunotherapeutics agents may be the answer to the enigma. The knowledge which can be obtained by those studies will be valuable in understanding other chronic infections, which with leprosy constitute a vast area for continuous research.

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LAS PRUEBAS SEROLOGICAS Y EL DIAGNOSTICO DE ENFERMEDADES INFECCIOSAS

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Resumen: Se ha tratado en una forma general de presentar las pruebas que hay hoy para el diagnóstico de enfermedades infecciosas por métodos serológicos agrupándolas primeramente por tipos de pruebas y luego por grupos de enfermedades. Se enfatiza la necesidad de tener dos muestras de suero por lo menos con 10 días de separación para interpretar una prueba. Es indispensable un aumento en título de 4 veces para ser significativo.

Summary: We have revised in a general format the serologic test available today for the diagnosis of infectious diseases. We have grouped the test first by types and then by group of diseases. It is not intended to be a review of every test available. We emphasize the need for two serum samples at least 12 days apart to interpret correctly the test. A four fold rise in titer is emphasized for diagnosis.

Introducción

Las pruebas serológicas en el diagnóstico de enfermedades infecciosas tienen un comienzo

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remoto, y las que tenemos en el presente son el resultado evolutivo de las pruebas originales. Se ha sofisticado la tecnología, pero las bases del diagnóstico serológico es la reacción entre un antígeno y un anticuerpo. Con estas pruebas tratamos de: (1) identificar el antígeno o anticuerpo relacionado etiológicamente al cuadro clínico del paciente y: 2) medir la respuesta inmunológica en contra del patógeno específico.

Las pruebas serológicas son usualmente pruebas confirmatorias y es indispensable comparar las titulaciones de dos pruebas serológicas para establecer la relación entre el cuadro clínico y el resultado serológico. Necesitamos suero agudo y un segundo suero, por lo menos de diez a catorce días más tarde, conocido como suero convalescente. La especificidad y sensibilidad de las pruebas serológicas varía; trataremos de presentar estas pruebas en una forma de aplicabilidad clínica. Nos proponemos presentar el diagnóstico serológico de infecciones por hongos, bacterias, virus, micoplasma y algunos parásitos.

Tipos de Pruebas

Las pruebas serológicas pueden ser directas indicando un antígeno o anticuerpo conocido y un anticuerpo o antígeno de prueba; o pueden ser pruebas indirectas (1).

Pruebas de Aglutinación, Hemaglutinación, Fijación, Latex y Flocculación

La prueba de aglutinación, es una directa, en la cual un antígeno no soluble se agrega con un anticuerpo. El suero del paciente se diluye seriamente y se mezcla con una concentración constante del antígeno de prueba; el título de anticuerpo es la dilución más alta del suero que produce aglutinación del antígeno. Estas pruebas pueden modificarse pegando el antígeno a una partícula como es una célula roja que ha sido expuesta al ácido tánico, resultando entonces en la prueba de hemaglutinación. Si el antígeno se pega a partículas inorgánicas entonces tenemos la prueba de Latex. La prueba puede revertirse y determinar si no hay aglutinación de las células rojas por el suero, si ésto ocurre, se puede determinar el título que inhibe la hemaglutinación (1).

Pruebas Indirectas

La prueba de fijación de complemento es un método indirecto. Durante una reacción antígeno anticuerpo uno o más de los constituyentes del complemento se consume. Esta mezcla de antígeno anticuerpo deficiente en complemento es incapaz de sostener una segunda reacción de antígeno anticuerpo. Se manifiesta desde el punto de vista del laboratorio por un fallo de la reacción a producir hemólisis de las células rojas. La prueba de fijación de complemento ha sido adaptada a una variedad de antígenos solubles, antígenos en formas de partículas y emulsiones. Una desventaja de la prueba de fijación de complemento es cuando el suero de algunos pacientes tiene actividad anticomplementaria y no puede interpretarse (1).

Pruebas de Neutralización

La habilidad de los anticuerpos para inactivar agentes biológicamente activos forma la base de la prueba de neutralización. Las técnicas de neutralización utilizaban en el pasado la administración de una mezcla de virus y anticuerpos a animales o huevos embrionados, con la muerte del animal o del embrión se indicaba la ausencia de anticuerpos neu-

tralizantes. Estos procedimientos ahora se llevan a cabo en sistemas de cultivos de tejidos e incluyen: 1) el medir la habilidad del anticuerpo para inhibir los efectos citopáticos en las monocamadas de células; 2) el determinar la inhibición metabólica, en donde los cultivos de tejidos infectados con un virus son capaces de generar una cantidad de ácido suficiente para producir un cambio en color que es un indicador que no se está produciendo anticuerpos neutralizantes, esto permite utilizar un proceso colorimétrico para medir la reacción y, 3) lo que se conoce como los ensayos de reducción en placas, en donde se mide la habilidad del suero para disminuir el número de placas que son producidas por una concentración específica de un virus (1).

Pruebas de Precipitina

En las pruebas de precipitina ocurre la interacción entre un antígeno y un anticuerpo produciendo un precipitado visible. Hay varios tipos de pruebas de precipitina entre las que se encuentran inmunodifusión, inmunoelectroforesis, y pruebas de inmunofluorescencia directa e indirecta. La inmunodifusión identifica los sistemas de antígeno y anticuerpo en la base de su habilidad para difundirse y precipitarse en un medio de una gelatina de agar.

En inmunoelectroforesis los antígenos y anticuerpos son separados de acuerdo a su movilidad electroforética una vez separados se deja que la precipitación ocurra (1).

En la inmunoelectroforesis en reverso, una corriente eléctrica se pasa a través del agar. Esto permite que el antígeno y el anticuerpo migren de direcciones opuestas y se produce una precipitación rápida al encontrarse (1).

Hay nuevas técnicas serológicas que utilizan la inmunofluorescencia. Las reacciones de antígenos y anticuerpos son inmunológicamente específicas, y la conjugación de un antígeno o anticuerpo a un fluorocromo tal como el isotiocianato de fluoresceína no altera su especificidad inmunológica o su reactividad. La detección de los antígenos más comunes en diagnósticos clínicos son por métodos de inmunofluorescencia como son las pruebas direc-

tas e indirectas de fluorescencia. La prueba directa de fluorescencia se lleva a cabo poniendo un anticuerpo que está marcado con fluoresceína directamente con el material que se va a examinar, como por ejemplo un frotis bacteriano o una secreción de tejidos o un cultivo de células. Si el antígeno está presente, el complejo antigénico anticuerpo fluoresceína se forma; esto puede entonces observarse microscópicamente con una luz ultravioleta (2).

En la prueba de fluoresceína indirecta, el material que se conoce que tiene el antígeno en particular se trata como un suero de prueba. Si el anticuerpo está presente se une al antígeno y se mantiene la laminilla. Se le añade entonces un segundo anticuerpo que es una antiinmunoglobulina marcada con fluoresceína y ésta reaccionará con el anticuerpo en el suero que se va a probar. El resultado de la reacción antígeno anticuerpo de prueba y antiinmunoglobulina fluoresceína puede detectarse con luz ultravioleta. Se puede utilizar un anticuerpo en contra de complemento en vez de un anticuerpo en contra de inmunoglobulina en esta prueba (2).

Pruebas de Radioinmunoensayo (3)

El radioinmunoensayo está basado en la competencia entre un antígeno marcado radioactivamente y varias diluciones de un antígeno de prueba no marcado para un número finito de moléculas de anticuerpo. La cantidad del antígeno marcado en la mezcla se conoce, por lo tanto la cantidad del antígeno de prueba presente se puede calcular.

Pruebas de Radioinmunoensayo por Enzimas (3)

El principio del inmunoensayo enzimático, tal como el que se conoce como la prueba inmunoabsorbente unida a enzimas ELISA, es similar a la prueba de inmunofluorescencia indirecta en principio. Después que anticuerpos antiinmunoglobulinas se añaden a una mezcla de un antígeno conocido y un suero de prueba, la antiglobulina se conjuga con una enzima, como es la fosfatasa alcalina.

Se añade un sustrato para que actúe la enzima. La reacción enzimática resultante puede medirse espectrofotométricamente y es proporcional a la cantidad de anticuerpos que se fija al antígeno.

Infecciones Causadas por Hongos

Histoplasmosis (4)

Histoplasma capsulatum puede ser difícil para aislar por métodos de cultivos tradicionales y las pruebas serológicas del suero, líquido cefalorraquídeo, plasma y líquido peritoneal son importantes en el diagnóstico de histoplasmosis. Se utilizan en las pruebas serológicas el antígeno de histoplasmina; micelial y el antígeno de la fase de levadura completa. Las pruebas frecuentemente usadas son de fijación de complemento, inmunodifusión y pruebas de aglutinación Latex. Estas dos últimas pruebas pueden llevarse a cabo solamente con histoplasmina, la fijación de complemento utiliza o puede utilizar ambos antígenos (3).

Los antígenos que fijan complemento al antígeno de la fase de levadura aparece de diez a veintidós días después de haber estado expuesto al hongo. Frecuentemente, para el tiempo que los síntomas de histoplasmosis pulmonar primaria han aparecido. En infecciones crónicas, anticuerpos al antígeno de levadura pueden estar disminuidos o ausentes, y los anticuerpos al antígeno de histoplasmina son de una importancia mayor. Un título de anticuerpos o fijación de complemento mayor o igual de uno a ocho se presume que indique una infección activa, pero la mayor parte de los pacientes con histoplasmosis tienen títulos mayores de 1:16. Algunos pacientes con infecciones severas pueden tener títulos más bajos.

Los títulos de anticuerpos disminuyen entre 1:8 a 1:16 varios meses después que la infección ha cesado. Un título persistente de 1:32 o mayor sugiere un pronóstico no favorable. Los anticuerpos que fijan complemento a *Histoplasma capsulatum* no son específicos, y reacciones positivas se pueden observar en blastomycosis y coccidioidomicosis.

Los resultados de estudios serológicos en

histoplasmosis pueden afectarse por la prueba de piel. Los anticuerpos se desarrollan como resultado de administrarse una prueba de piel en 10 al 20 por ciento de los pacientes con reacciones positivas y están dirigidos principalmente en contra de los antígenos de histoplasmina. Los anticuerpos aparecen entre los primeros quince días y pueden permanecer elevados por un período hasta de seis meses. El título de anticuerpos inducidos por la prueba de piel es usualmente no mayor de 1:32. La prueba de piel tiene muy poca utilidad en el diagnóstico de histoplasmosis aguda. En infección aguda, el título de anticuerpo puede ser negativo o bajo. Si el título de anticuerpos en fase convalescente se encuentra más tarde elevado, esto puede ser un reflejo de la prueba de piel que se administró o de histoplasmosis activa. La prueba de piel de histoplasmosis es solamente útil en la evaluación de alergia cutánea y también en enfermedad cavitaria del pulmón en individuos que tienen pruebas de tuberculina negativa.

Para ayudar a resolver el problema clínico se puede hacer pruebas de inmunodifusión y estudiar las líneas de precipitación M (myceliales) y las H (histoplasmina). La banda M en la prueba de inmunodifusión la cual aparece temprano en el curso de histoplasmosis, puede persistir a pesar de que el paciente esté asintomático y puede inducirse por la prueba de piel. La banda H, usualmente está asociada con infección activa y no se afecta por la prueba de piel. Por lo tanto, en una prueba de inmunodifusión la banda H es mucho más útil (4).

La prueba de aglutinación de Latex es rápida, pero es un método poco sensitivo para el diagnóstico de histoplasmosis. Cuando la prueba de aglutinación de latex es positiva, la prueba de fijación de complemento debe llevarse a cabo para confirmar este diagnóstico. La combinación de una prueba de inmunodifusión y una prueba de fijación de complemento nos da el rendimiento mayor para lograr un diagnóstico certero de histoplasmosis aguda. En histoplasmosis pulmonar crónica y en enfermedad inactiva, las pruebas serológicas son positivas en menos de la mitad de los pacientes; la prueba de piel están positivas en el 97 por ciento de ellos (4, 5, 6).

Cryptococcosis (6)

Técnicas serodiagnósticas que sean confiables para el diagnóstico de meningitis criptocócica son extremadamente importantes, ya que el examen del líquido cefalorraquídeo con tinta china es poco sensitivo, y el cultivo de *Cryptococcus neoformans* puede ser difícil. La prueba de aglutinación de Latex para el antígeno de criptococco es rápida y exacta. El antígeno puede ser detectado en el líquido cefalorraquídeo. La concentración del antígeno reflejada por la titulación de anticuerpos en el líquido cefalorraquídeo disminuye con la administración de anfotericina B en dosis adecuadas.

A pesar de que la prueba de aglutinación de Latex para antígeno de criptococo es específica, pueden ocurrir falsos positivos en individuos con artritis reumatoidea y leucemia linfocítica crónica. Debe de ordenarse una prueba de factor reumatoideo en todos los pacientes en donde se ha demostrado el antígeno criptococo. En pacientes con meningitis criptocócica se encuentran entre cinco al quince por ciento de falsos negativos utilizando esta prueba.

Las pruebas de anticuerpo anticriptocócico son ocasionalmente útiles cuando las pruebas de antígeno son negativas. La presencia de anticuerpos indica mejoría, y se puede encontrar el anticuerpo comunmente en el tiempo cuando los títulos de antígenos están disminuyendo (5, 6).

Candidiasis

Las especies de *Candida* pueden ser responsables por infecciones en pacientes que tengan comprometidas sus defensas locales o sus defensas sistémicas. Infecciones por *Candida* pueden ser tratadas si se reconocen temprano, pero el diagnóstico de *Candidiasis* es difícil de establecer cuando se utilizan técnicas de cultivo y de tinción. La presencia de precipitina dirigida en contra de los antígenos citoplásmicos de *Candida* pueden ser un indicador útil de infección diseminada por *Candida*, ya que la prueba de precipitina es muy específica. Esta prueba carece de sensibilidad y es negativa en 25 por ciento al 40 por ciento de los pacientes con *Candidiasis*, por lo tanto, tenemos una prueba que es específica pero muy poco sensitiva (7).

A pesar de que los anticuerpos aglutinantes en contra de *Candida* pueden detectarse en infecciones sistémicas por *Candida* y en individuos saludables. La presencia de ambas, aglutininas y precipitinas, es más sugerible de infecciones serias que la presencia aislada de precipitinas o aglutininas. La prueba de dispersión en el tubo germinal, en donde un anticuerpo IgG inhibe la aglutinación de filamentos de *Candida albicans*, puede que sea la prueba más específica en Candidiasis diseminada más no está en todos los laboratorios. Una prueba fluorescente para Candidiasis está siendo estudiada y puede ser que sea útil en un futuro (7).

Las pruebas de piel no tienen ningún valor en Candidiasis; 80 por ciento de individuos normales desarrollan reacciones de piel positiva al antígeno de *Candida* (5).

Coccidioidomycosis

Coccidioides immitis puede ser cultivado relativamente fácil, pero las pruebas de piel y los métodos serológicos pueden ser útiles en el diagnóstico de coccidioidomycosis. Los títulos de anticuerpos pueden ser afectados por las pruebas de piel. Una prueba positiva de piel se desarrolla de una a tres semanas después de exposición al hongo.

El antígeno coccidioidin, es un filtrado de un cultivo de *Coccidioides immitis* en las fase micelial. El suero, plasma, líquido ascítico, líquido pleural y líquido sinovial puede ser probado para la presencia del anticuerpo. Hay una serie de reacciones cruzadas entre coccidioidin, histoplasmin y los antígenos de *Blastomyces dermatidis* (6).

Hay cuatro pruebas serológicas en el diagnóstico de coccidioidomycosis. La precipitación en tubo, la aglutinación Latex, la inmunodifusión y la fijación de complemento. La prueba de precipitación en tubo y la prueba de aglutinación Latex son útiles en la enfermedad aguda y en exacerbaciones agudas de infecciones crónicas. Las pruebas de precipitinas en tubo son posibles y pueden detectarse en el 80 por ciento de los pacientes en las primeras dos semanas después que los síntomas aparecen, pero están ausentes en el 90 por ciento después de seis meses. La prueba de precipitina en tubo es altamente específica. A pesar de que la prue-

ba de aglutinación Latex es rápida y sensitiva, carece de especificidad, y, cuando es positiva, debe de confirmarse por otra prueba. La prueba de inmunodifusión se convierte en positiva más tarde que la prueba de aglutinación de Latex y las pruebas de precipitina en tubo. Debe de confirmarse por una prueba de fijación de complemento. La prueba de inmunodifusión es sensitiva, pero no específica (5, 6).

La prueba de fijación de complemento se convierte en positiva de cuatro a seis semanas después que comienza la enfermedad clínica. La respuesta máxima está presente después de dos a tres meses. A pesar de que la prueba de fijación de complemento en una titulación igual o mayor de 1:2 puede ser indicativa de enfermedad activa, títulos más altos se observan usualmente en infecciones severas. Un título de anticuerpos es mayor de 1:16 en el 80 por ciento de los individuos con coccidioidomycosis diseminada. La prueba de piel usualmente es negativa en el momento cuando la prueba de fijación de complemento es positiva. Un signo de pronóstico favorable se sugiere cuando la prueba de piel se convierte en positiva y el título de fijación de complemento baja. A pesar de la seropositividad, aproximadamente 25 por ciento de los pacientes con meningitis coccidioidal tienen pruebas negativas de fijación de complemento en el líquido cefalorraquídeo (5, 6).

La combinación de varias pruebas es superior a cualquier procedimiento sencillo en coccidioidomycosis. La combinación de inmunodifusión con aglutinación latex, o fijación de complemento con precipitinas en tubo son positivas en el 85 por ciento al 93 por ciento de los pacientes que se han demostrado más tarde tener coccidioidomycosis. En el futuro puede que se utilicen pruebas de fluorescencia de anticuerpo en estos pacientes (5, 6).

Blastomycosis

A pesar de que las pruebas de fijación de complemento se han utilizado en el diagnóstico de blastomycosis, las reacciones son transitorias e inconsistentes, y hay una incidencia alta de reactividad cruzada y la sensibilidad de éstas son pobres. No hay un antígeno para pruebas de piel. Las pruebas de difusión en agar y la prueba de anticuerpos fluo-

rescentes puede que se utilicen en el futuro, pero en el momento están en desarrollo (6).

Aspergillosis

Las especies de *aspergillus* se identifican fácilmente por tinciones y métodos de cultivos. Estos hongos son ubicuitos, y es difícil de establecer un diagnóstico de aspergillosis, ya que el organismo puede aislarse de individuos saludables de la misma manera de individuos que están infectados.

La prueba de difusión en gelatina de agar, en donde se detectan precipitinas en el suero es una técnica útil en el diagnóstico de ciertas formas de aspergillosis. Las precipitinas están presentes en casi 100 por ciento de los pacientes con aspergillomas y en el 70 por ciento de los pacientes con aspergillosis pulmonar alérgica. Las precipitinas están rara vez presentes en individuos no infectados, pero aproximadamente 40 por ciento de los pacientes con tuberculosis pulmonar demuestran estos anticuerpos. La prueba de inmunoelectroforesis en reverso aumenta la velocidad y sensibilidad de las pruebas de precipitina. Las pruebas serológicas no son útiles en aspergillosis invasiva. Una prueba de fluorescencia indirecta está siendo evaluada (6).

Otras Infecciones por Hongos

No hay técnicas de serodiagnóstico para el diagnóstico de actinomicosis. Técnicas de anticuerpos fluorescentes pueden utilizarse para identificar ciertos actinomicetos en cultivos, en tinciones de tejidos y exudados (5, 6).

Anticuerpos precipitantes, pueden detectarse por inmunodifusión y aparecen temprano en el curso de paracoccidioidomycosis (*Blastomycosis* suramericana). Los anticuerpos que fijan complemento se desarrollan más tarde y persisten por un tiempo más largo que los anticuerpos precipitantes. Las pruebas de fijación de complemento tienen unas titulaciones más altas en infección diseminada; y los títulos empiezan a disminuir cuando el paciente comienza a responder al tratamiento.

Las pruebas de aglutinación en tubos y aglutinación latex para esporotricosis puede que sean

más específicas y sensitivas y hay algunas de ellas que se utilizan en el diagnóstico de esporotricosis. En el futuro, una prueba de fluorescencia de anticuerpos puede que se utilice para identificar *Sporotrichum schenckii* en materiales clínicos y en cultivos (5, 6).

Pruebas Serológicas para el Diagnóstico de Infecciones por Viruses (8)

Mononucleosis Infecciosa (9)

Los títulos elevados de anticuerpos heterófilos que aglutinan las células rojas de carnero, se desarrollan en pacientes con mononucleosis infecciosa. Anticuerpos similares pueden estar presentes en otras infecciosas, en enfermedad del suero y en individuos normales.

La prueba diferencial de heterófilos se emplea en el diagnóstico de mononucleosis infecciosa y se basa en dos propiedades específicas de las células rojas del carnero para aglutinarse en mononucleosis infecciosa; 1) los anticuerpos no son completamente removidos por la absorción con antígeno de riñón de cobayo, y 2) los anticuerpos son fácilmente absorbidos por células rojas vacunas. Los anticuerpos aglutinantes presentes en la enfermedad del suero se absorben ambos por las células de riñón de cobayo y por las células rojas de ganado vacuno.

Una prueba enzimática de hemolisina con eritrocitos de ganado vacuno se ha utilizado en el diagnóstico de mononucleosis infecciosa. El desarrollo reciente más importante ha sido la prueba de "Monospot"® (10, 11). Una suspensión salina al 4 por ciento de células rojas de caballo se utiliza como antígeno. Cuando una gota del antígeno se añade al suero, ocurre granulación gruesa indicando una reacción positiva. Esta técnica es rápida, específica y sensitiva.

La positividad de las pruebas de las aglutininas heterófilas "Monospot"® se desarrolla concomitantemente: aproximadamente 40 por ciento de los pacientes con mononucleosis infecciosa tienen pruebas positivas durante la primera semana de la enfermedad; 80 por ciento son positivos para la tercera semana. La prueba "Monospot"® usualmente es suficiente para establecer el diagnóstico de mo-

nonucleosis infecciosa. Cuando las manifestaciones clínicas son atípicas, el diagnóstico diferencial utilizando la prueba de heterófilo debe también llevarse a cabo (10, 11).

Ocasionalmente, una prueba negativa de heterófilos puede observarse en pacientes con hallazgos que sugieren mononucleosis infecciosa. En esta situación, el diagnóstico debe de confirmarse por la utilización de estudios serológicos para determinar la causa de mononucleosis infecciosa, el virus de Epstein Barr. La enfermedad puede ser producida por otros agentes desde el punto de vista de cuadro clínico, como son los citomegalovirus y debe de confirmarse también serológicamente si este fuera el caso (10, 11).

Rubella (12)

Durante el curso de rubella, se desarrollan anticuerpos IgM primeramente. Estos anticuerpos están presentes transitoriamente. Los anticuerpos IgG aparecen más tarde y pueden cruzar la placenta durante los segundos y terceros trimestres del embarazo. Los anticuerpos IgM se producen tarde en la gestación por el feto infectado por rubella. Por lo tanto, al nacer, la sangre de un neonato infectado puede contener IgG de la madre y IgM producido por el recién nacido. El IgG de origen materno se pierde durante el período temprano post parto; el IgM puede persistir a niveles altos hasta el segundo año de edad.

Las pruebas de inhibición de hemaglutinación y de fijación de complemento y neutralización se han utilizado en el diagnóstico de rubella. Las pruebas de hemaglutinación no distinguen entre IgM y IgG, pero la ausencia de anticuerpos que inhiben la hemaglutinación en la sangre del cordón fetal hacen el diagnóstico de rubella muy poco probable. Si se encuentra una prueba de hemaglutinación positiva cuando el niño nace, pero estos títulos disminuyen durante los primeros seis meses de edad lo que sugiere es transferencia pasiva de anticuerpos maternos en vez de una infección intraparto. La persistencia o aumento de los anticuerpos que inhiben hemaglutinación durante el primer año de vida indican infección congénita con rubella. La IgM puede distinguirse de la IgG por inmunofluorescencia.

La infección congénita con rubella se sugiere fuertemente por la presencia de IgM en la sangre del cordón fetal (12).

El diagnóstico serológico puede utilizarse para: 1) evaluar mujeres embarazadas que han estado expuestas a rubella; 2) detectar mujeres que sean susceptibles a rubella para los propósitos de vacunación, y 3) determinar respuesta a vacuna. Un individuo debe de considerarse susceptible a infección cuando los títulos de anticuerpos de inhibición de hemaglutinación son menores o iguales a 1:8 en los primeros 10 días después de haber estado expuesto. Un título más alto implica inmunidad absoluta. Un aumento de cuatro veces en los títulos de anticuerpos de inhibición de hemaglutinación en un individuo susceptible indican una infección reciente (12).

Reinfección con rubella puede ocurrir cuando un individuo que ha estado inmune como resultado de infección primaria o inmunización se reexpone al virus. Reinfección se manifiesta en un aumento de cuatro veces en los títulos de un nivel de anticuerpos pre-existente. Esto es menos frecuente en individuos que han estado vacunados, y probablemente no ocurra en individuos que tengan títulos de anticuerpos de inhibición de hemaglutinación mayores de 1:64. Viremia es rara en reinfección. Transmisión transplacentaria del virus es poco probable (12).

Una prueba de hemólisis en gelatina puede ser la más sensitiva y reproducible para detectar inmunidad por rubella pero ésta, está en desarrollo (12).

Rubeolla (13)

Aproximadamente 14 días después de exponerse al virus de rubeolla, se desarrolla una erupción, y anticuerpos neutralizantes que fijan complementos y de inhibición de aglutinación pueden detectarse en esos momentos. Los anticuerpos de inhibición de hemaglutinación pueden persistir por años y son medidores confiables de inmunidad.

La panencefalitis subaguda esclerosante, una enfermedad progresiva, degenerativa, e invariablemente fatal del sistema nervioso central que ocurre en

la adolescencia se cree que sea una recrudescencia de sarampión. Anticuerpos en contra de sarampión son detectados en todos los pacientes con panaencefalitis subaguda esclerosante, incluyendo aquellos que no han tenido una infección o vacunación documentada con sarampión. Los anticuerpos IgM están presentes en el suero y pueden persistir hasta la muerte. El anticuerpo IgM usualmente desaparecen después de dos meses de infección con sarampión agudo. Ambos anticuerpos IgM y IgG pueden detectarse en el líquido cefalorraquídeo de los pacientes con panaencefalitis esclerosante subaguda.

Hepatitis (14)

Las pruebas de inhibición de hemaglutinación y fijación de complemento se usaban a principio para medir el antígeno B de superficie. Estas pruebas eran específicas, pero le faltaba sensibilidad. La prueba de radioinmunoensayo provee mayor sensibilidad.

La determinación del antígeno B de superficie se utiliza en la evaluación de pacientes con hepatitis aguda y crónica, pero se usa más frecuentemente en la investigación de donantes potenciales de sangre. A pesar de que el radioinmunoensayo detecta de dos a diez veces más individuos con antígeno B de superficie se utiliza en la evaluación de pacientes con hepatitis aguda y crónica, pero se usa más frecuentemente en la investigación de donantes potenciales de sangre. A pesar de que el radioinmunoensayo detecta de dos a diez veces más individuos con antígeno B de superficie positivo que lo que detectaban las pruebas anteriores, aproximadamente dos terceras partes de los casos de hepatitis asociada de transfusión, es transmitida por sangre que es negativa para la presencia de antígeno B de superficie. La razón para esta discrepancia puede deberse a que hay otro agente que pueda ser responsable por esta infección, o como el resultado de que las pruebas serodiagnósticas para determinar la presencia del marcado de hepatitis B no sean suficientemente sensitivas.

El anticuerpo en contra del centro de hepatitis B, lo que se conoce como HBc (AB) se puede detectar por prueba de fijación de complementos.

to, usualmente desaparece después que el paciente ha recobrado de hepatitis B, pero persiste en los portadores del antígeno B de superficie.

Pruebas serodiagnósticas para hepatitis A detectando anticuerpos de IgG y IgM están en el momento siendo utilizadas en muchos laboratorios (14).

Pruebas Serológicas para el Diagnóstico de Infecciones Parasitarias (15, 16)

Amebiasis (17)

El método más efectivo del diagnóstico de amebiasis intestinal es el examen de las heces. Como muchas veces el examen de heces es técnicamente difícil y conocemos que en amebiasis hepática las amebas fácilmente están ausentes de las heces, las pruebas serológicas se han convertido en un método importante en el diagnóstico de infecciones por *Entamoeba histolytica*. Los anticuerpos pueden detectarse por precipitación, por difusión en gelatina o por pruebas de hemaglutinación indirecta en tanto como el 95 por ciento de los pacientes con abscesos hepáticos y el 85 por ciento de los pacientes con amebiasis intestinal. Difusión en acetato celular, una modificación de la prueba de precipitina por difusión en gelatina, puede utilizarse para el diagnóstico rápido en infecciones donde la vida del paciente está en juego.

Toxoplasmosis (18, 19)

Toxoplasma gondii puede producir enfermedad diseminada, coriorretinitis, y enfermedad congénita. Este microorganismo ubicuo puede también ser responsable por una condición que se parece a la mononucleosis infecciosa caracterizada por linfadenopatía, fiebre, malestar, y otros síntomas constitucionales. El diagnóstico de toxoplasmosis usualmente depende de pruebas serológicas, ya que la aislación de ese microorganismo es extremadamente difícil y costosa. Los métodos que se emplean son la prueba de Sabin-Feldman, la de fijación de complemento, la de inmunofluorescencia indirecta y la prueba de hemaglutinación indirecta.

Toxoplasma gondii se tiñe con azul de metileno, excepto cuando el organismo ha sido previamente expuesto a anticuerpos en contra de toxoplasma. Esta observación forma la base para la prueba de tinción de Sabin Feldman. Esta prueba es específica. Hay métodos alternos de diagnóstico que se han desarrollado porque esta prueba es costosa y tiene el problema de que se utilizan con microorganismos vivos. La prueba de fijación de complemento es útil en el diagnóstico de toxoplasmosis adquirida. La prueba de hemaglutinación indirecta consume mucho tiempo, pero es específica. La prueba de fluorescencia indirecta es específica y sensitiva. Hay una prueba de fluorescencia en la que se utilizan anticuerpos IgM y estos aparecen durante la primera semana de la enfermedad y llegan a la concentración máxima en el primer mes. Un título de mayor o igual de 1:80 o un aumento de dos veces en el título indican una infección reciente (18).

La prueba de Sabin Feldman y la prueba de fluorescencia indirecta tienen títulos usualmente de más de 1:1000 cuando toxoplasmosis se desarrolla en un individuo inmunocomprometido (18, 19).

Anticuerpos en el suero de un recién nacido pueden resultar de dos lugares: 1) de infección o, 2) de transferencia pasiva de anticuerpos maternos. La persistencia o un título de anticuerpos que aumentan de 2 a 3 meses después del nacimiento o títulos altos en el nacimiento en un niño con evidencia crónica de toxoplasmosis, indican infección congénita. La prueba de fluorescencia indirecta por la cual se mide IgM, es más específica en toxoplasmosis congénita. La prueba indirecta de hemaglutinación y de fijación de complemento son falsamente negativas en esta condición.

Las pruebas serológicas del humor acuoso, en vez de sangre, pueden ser útiles en el diagnóstico de coriorretinitis causada por toxoplasmosis (19).

Trichinosis (17, 19)

El diagnóstico de trichinosis se basa usualmente en un historial de haber consumido cerdo o alguna otra carne contaminada, y el hallazgo de dolor muscular, eosinofilia, y la identificación del pa-

rásito en una biopsia de un músculo. La prueba de aglutinación de latex y la prueba de fijación de complemento frecuentemente son negativas temprano en el curso de trichinosis. El tratamiento inmediato puede requerirse en infecciones severas, la mayor utilidad de las pruebas serológicas en trichinosis es para confirmar el diagnóstico que ha sido establecido por otros métodos. La prueba de aglutinación de latex es sensitiva, pero hay que reconocer que reacciones falsamente positivas pueden observarse en pacientes con tuberculosis.

Equinococosis (17, 18)

Las pruebas serológicas más efectivas en el diagnóstico de equinococosis son las pruebas de hemaglutinación indirecta y la prueba de piel de Casini. Ambas son sensitivas. La prueba de hemaglutinación indirecta es más específica, es positiva en aproximadamente 90 por ciento de los pacientes que tienen quistes hepáticos y en el 30 por ciento de aquellos con quistes en los pulmones. A pesar de que la prueba de fijación de complemento no es tan sensitiva, es útil en la evaluación postoperatoria de equinococosis. Otras pruebas serológicas permanecen positivas postoperatoriamente, pero la prueba de fijación de complemento se convierte en negativa después de cirugía. Una disminución significativa en títulos en pruebas de fijación de complemento indican cura quirúrgica; un título que no cambia o que aumenta sugiere persistencia o recurrencia de la infección. Las pruebas de anticuerpos fluorescentes son también una técnica sensitiva.

Pruebas Serológicas para el Diagnóstico de Infecciones Rickettsias

Rickettsias (20)

Los anticuerpos se desarrollan relativamente tarde en el curso de la fiebre manchada de las montañas rocallosas y, debido a que el tratamiento antibiótico no debe retardarse, la función de las técnicas para el diagnóstico serológico son confirmatorias en vez de diagnósticas. Los anticuerpos pue-

den primeramente detectarse por el método de Weil-Felix, entre los días 8 a 12 de la enfermedad. En esta prueba, el suero de un paciente con enfermedad de las montañas rocallosas aglutina una suspensión de *Proteus* OX-19 que comparte un antígeno con *Rickettsia rickettsi*. La prueba de Weil-Felix ha sido reemplazada con una prueba de fijación de complemento que es específica para las infecciones de las fiebres manchadas. El uso temprano de antibióticos puede suprimir la respuesta a una prueba de fijación de complemento.

Ambos, una prueba indirecta de hemaglutinación y una prueba indirecta de fluorescencia puede ser que sea superior a la prueba de fijación de complemento en tifus y en enfermedad de las montañas rocallosas. La prueba indirecta de fluorescencia puede ser modificada para detectar IgM; esto puede ser útil en el diagnóstico de infecciones recientes.

Pruebas Serológicas para el Diagnóstico de Infecciones Bacterianas por *Salmonella*

La reacción de Widal's puede utilizarse para el diagnóstico de infecciones producidas por *Salmonella*. La aglutinina dirigida en contra de los antígenos somáticos O o de los antígenos flagelares H pueden detectarse después de la primera semana de una fiebre inducida por *Salmonella*; éstos obtienen sus concentraciones más altas entre la tercera y cuarta semana de infección. Un aumento de cuatro veces o mayor en los títulos de aglutinación en individuos no inmunizados sugiere la posibilidad de infección. La prueba de Widal's carece de sensibilidad y especificidad. *Salmonella typhi*, la especie más comunmente responsable por fiebres entéricas, comparte uno o más antígenos con todas las otras *Salmonellas* del grupo D, y reactividad cruzada es frecuente y común. Los antígenos que se han utilizado en la prueba de Widal son pobremente estandarizados. Se ha sugerido que la prueba de floculación de colesterol utilizando el antígeno O puede ser más específica y sensitiva. La prueba de hemaglutinación para el antígeno G' se ha utilizado para detectar y para rastrear los portadores de tifoidea, pero su utilidad es limitada, porque los pacientes con

fiebres entéricas pueden también desarrollar anticuerpos a este antígeno.

Brucellosis y *Plaga* (17)

El diagnóstico de *Brucellosis* y *Plaga* puede establecerse por el aislamiento del microorganismo, ya que la interpretación de pruebas de aglutinina para brucelas y *Francisella tularensis* se hace difícil por la reactividad cruzada de estos dos microorganismos con el de *Vibrio cholerae*.

Leptospirosis (1, 17)

La serología para leptospira se lleva a cabo solamente en laboratorios selectos, porque se utilizan organismos vivos como antígenos para la prueba de aglutinación. Una prueba indirecta de hemaglutinación para leptospirosis se ha empleado recientemente. Estas pruebas deben de hacerse rutinariamente en los pacientes donde se sospecha la enfermedad utilizando una prueba aguda en la primera semana de enfermedad y repitiéndole diez a catorce días más tarde.

Infecciones neumocócicas, estafilocócicas y por *Hemophilus influenzae* (22)

Los neumococos en especímenes clínicos se han demostrado por la reacción de Quellung. En esta prueba la cápsula de neumococos y un anticuerpo específico interaccionan para producir hinchazón de la cápsula que puede observarse microscópicamente.

La inmunoelectroforesis en reverso no requiere la presencia de organismos vivos, y esta técnica puede ser útil: (1) en pacientes que han recibido antibióticos previamente, (2) evaluando especímenes que contengan formalina o que hayan sido enviados a través del correo, (3) en caso en donde los cultivos rutinarios no han sido efectivos para recuperar el microorganismo. Esta prueba de inmunoelectroforesis en reverso ha sido comparada a la técnica de cultivo y de microscopía directa en el diagnóstico de meningitis bacteriana. Se ha encontrado que los cultivos bacterianos son la forma más sen-

sitiva para hacer el diagnóstico detectando el 85 por ciento de los casos (23, 24). La prueba de inmunoelectroforesis en reverso es positiva en solamente el 55 por ciento de los pacientes con meningitis bacteriana (24). La continuación de la prueba de inmunoelectroforesis en reverso y de microscopía directa es equivalente al cultivo solamente.

Si se concentran muestras de orina, estas pueden ser investigadas por inmunoelectroforesis en reverso. Esta técnica produce reacciones falsamente positivas. Los anticuerpos que se utilizan en el momento en la inmunoelectroforesis en reverso incluyen un antisuero neumocócico polivalente, un antisuero meningocócico polivalente, y un antisuero en contra de *hemophilus influenzae* tipo B y anticuerpos en contra de *Hemophilus* polivalente. Inmunoelectroforesis en reverso de suero y orina se ha utilizado para detectar bacteremia neumocócica en pacientes con pulmonía neumocócica (24).

La inmunoelectroforesis en reverso para medir anticuerpos dirigido en contra de ácidos teicóicos, un constituyente mayor de la pared celular de *Staphylococcus aureus* se ha utilizado en el diagnóstico de infecciones estafilocócicas severas, particularmente endocarditis. A pesar de que la presencia de anticuerpos en contra de ácidos teicóicos parecen distinguir entre los pacientes que tienen endocarditis estafilocócicas y aquellos que tienen endocarditis producida por otras bacterias, los pacientes con bacteremia estafilocócica sin endocarditis no se pueden distinguir de aquellos que tengan endocarditis. La medida de anticuerpos en contra de ácidos teicóicos puede ser útil cuando los cultivos en el paciente en el cual se sospecha una infección estafilocócica se han convertido en negativos por tratamiento antibiótico previo, o cuando el tratamiento debe instituirse en pacientes seriamente enfermos antes de que los resultados de los cultivos estén listos (22).

Una prueba de hemaglutinación en latex se ha utilizado para detectar antígenos bacterianos en el líquido cefalorraquídeo, sangre y en concentrados de orina. Esta técnica es rápida y específica y puede que resulte ser más sensitiva que electroforesis en reverso (22).

El título de antiestreptolisina O "ASO", una prueba de neutralización puede ser útil en el diagnóstico de fiebre reumática aguda. Estreptolisina O se combina con el suero del paciente, se añaden células rojas, y ocurre hemólisis cuando el anticuerpo está presente. Anticuerpos en contra de la hemolisina O o estreptolisina O aparecen aproximadamente 7 días después del comienzo de una faringitis estreptocócica aguda, llegan a sus niveles máximos de dos a cuatro semanas más tarde, y pueden permanecer en títulos altos por semanas a meses. Un título que sube sugiere una infección reciente. Un título estable, a pesar de su nivel indica una infección estreptocócica o indica una exposición estreptocócica previa. Títulos que aumentan, se observan en el 70 al 80 por ciento de los individuos con faringitis estreptocócicas pero menos frecuentemente en individuos con infecciones de piel estreptocócicas. En epidemias, la mayor parte de los niños con faringitis estreptocócicas que no han recibido penicilina demuestran un aumento significativo en los títulos "ASO", pero en infecciones esporádicas, solamente la mitad de estas personas demuestran estos títulos. La prueba "ASO" puede ser falsamente positiva en individuos con enfermedad hepática. Anticuerpos en contra de otra enzima estreptocócica, "DNasaB" pueden ser detectados en pacientes que tengan infecciones de piel estreptocócicas cuando la prueba "ASO" es negativa. La prueba de estreptozima mide anticuerpos dirigidos en contra de cinco enzimas estreptocócicas, estreptolisina O, DNasaB y hialuronidasa, estreptokinasa, y la nucleotida de adenina nicotamínica. Esta prueba es más sensitiva que la prueba "ASO" y puede ser más útil en el diagnóstico de glomerulonefritis postestreptocócica y fiebre reumática aguda. La prueba de estreptozima puede ser una manera útil de hacer el diagnóstico o podría considerarse un reemplazo en la prueba de "ASO" en el diagnóstico de infecciones estreptocócicas irrespectivo del lugar en que ocurran.

Frotis de exudados faríngeales y cultivos tempranos de faringe pueden ser teñidos por anticuerpos fluorescentes dirigidos en contra del carbohidrato C del estreptococo grupo A y otros estreptococos. El resultado de estas tinciones puede correlacionar con cultivos subsiguientes pero está en una fase investigativa (25).

Pruebas Serológicas en el Diagnóstico de Enfermedades Venéreas

Sífilis (26)

Las pruebas serológicas en el diagnóstico de sífilis incluyen pruebas treponémicas y no treponémicas. Las pruebas no treponémicas detectan reagentas, un complejo de globulinas que aparecen temprano en el curso de sífilis. Los títulos de reagina disminuyen o desaparecen después de tratamiento y pueden espontáneamente disminuir a través de un período largo de tiempo en pacientes no tratados. Dos métodos se utilizan para documentar la presencia de reagina, estos son la prueba de Wasserman que es una prueba de fijación de complemento y la prueba de VDRL una prueba de floculación que mide la habilidad de un suero inactivado para agregar una suspensión de un antígeno de cardio-lipina-lecitina. Las pruebas no treponémicas (28) no distinguen entre una reagina producida por sífilis y la globulina anormal presente en individuo con falsos positivos biológicos, que pueden ser transitorios en varias enfermedades febriles o persistentes en lepra, enfermedad del colágeno, sarcoidosis, y en adicción a drogas. Las pruebas no treponémicas son insensitivas y no específicas; del 25 al 30 por ciento de los pacientes con sífilis primaria, tardía o latente tienen prueba de VDRL negativa. La prueba de Reagina Plasmática Rápida "RPR" ha reemplazado la prueba de VDRL en muchos laboratorios. En este método, partículas de carbón se añaden al antígeno de VDRL, y puede observarse floculación en una tarjeta plástica. La prueba "RPR" es más conveniente que la VDRL y es igualmente sensitiva y específica que esta otra.

Debido a que las pruebas no treponémicas permiten cuantitizar los resultados, pueden utilizarse para determinar la respuesta a tratamiento. La mayor parte de los pacientes que han recibido tratamiento adecuado para sífilis primaria se convierten en seronegativos. Un número más pequeño reierte a seronegatividad después del tratamiento para sífilis secundaria. La mayor parte de los pacientes con sífilis tardía o latente se conocen como seropersistentes. Esto es que a pesar de haber sido tratados adecuadamente sus pruebas serológicas per-

sisten positivas.

La prueba de anticuerpos de fluorescencia se ha utilizado para medir anticuerpos treponémicos específicos. Estas técnicas se han modificado para aumentar especificidad de las pruebas de dilución de suero y en lo que se conoce como la prueba FTA-ABS o la prueba absorbente de FTA. La prueba de inmovilización de treponemas que detecta anticuerpos que disminuyen la velocidad de movilidad de *Treponema pallidum* vivo se ha utilizado como un estándar de especificidad.

Las pruebas treponémicas específicas como son las de anticuerpos fluorescentes o FTA permanecen positivas a pesar de que el paciente haya recibido un tratamiento adecuado de antibióticos, y no son útiles en determinar respuesta a tratamiento. Estas técnicas son más sensitivas que las pruebas no treponémicas en las bases tempranas, tardía y latente sífilis. Las pruebas de VDRL y RPR se emplean como pruebas de rastreo. Si una de estas es positiva, entonces debe utilizar la prueba de FTA-ABS, la prueba de fluorescencia de absorción para confirmar el diagnóstico de sífilis (26, 27, 28).

El diagnóstico de neurosífilis se establece cuando la prueba de VDRL o RPR del líquido cefalorraquídeo es positiva. La sensibilidad de la prueba FTA-ABS, del líquido cefalorraquídeo en neurosífilis no se ha demostrado (26, 27, 28).

El material que se obtiene de lesiones húmedas o de nódulos linfáticos es evaluada por una técnica de anticuerpos fluorescentes en el examen de campo oscuro. Este método tiene su utilidad más grande en el diagnóstico de sífilis primaria y ocasionalmente útil en sífilis secundaria. Las pruebas directas de fluorescencia pueden también llevarse a cabo. Esta prueba utiliza anticuerpos dirigidos específicamente en contra de *Treponema pallidum* y puede emplearse para evaluar lesiones en la mucosa oral. Anticuerpos no específicos utilizados en la prueba de campo oscuro pueden detectar treponemas otras que no sean *Treponema pallidum* que usualmente son miembros normales de la microflora oral (28).

La habilidad del suero de un paciente con sífilis para aglutinar células rojas tratadas con ácido tánico que han sido previamente recubiertas de antígenos de *Treponema pallidum* forman bases para la prueba de microhemaglutinación para *Treponema*

ma pallidum conocida como MHA-TP. Esta prueba está disponible en algunos laboratorios de referencia (28).

Gonorrhea (29)

El aislamiento de *Neisseria gonorrhea* de lugares genito-uritarios o de otros lugares por los métodos establecidos es la base para el diagnóstico de infecciones gonocócicas. Métodos serológicos aplicables a poblaciones grandes podrían ser útiles, ya que los cultivos ocasionalmente falsos negativos, y cultivos para programas en masas son extremadamente costosos.

Una prueba de fluorescencia indirecta, una prueba de aglutinación latex y una prueba de microfloculación se han desarrollado para el diagnóstico de gonorrhea; todas han estado asociadas con una alta incidencia de falsos positivos y falsos negativos y en el momento no son pruebas que se utilizan rutinariamente en este diagnóstico y están simplemente bajo investigación.

Pruebas Diagnósticas en el Diagnóstico de Infecciones por *Mycoplasma* (17)

Las aglutininas frías activamente aglutinan las células rojas humanas del grupo O o 4^o C, pero no a 37^o (Palmer). Durante la segunda a cuarta semana de la enfermedad en pacientes con infecciones causadas por *Mycoplasma pneumoniae* aproximadamente 50 por ciento de estos pacientes desarrollan un título de aglutinina fría significativa que usualmente desaparece para la sexta a octava semana. Las aglutininas frías pueden detectarse en un número de condiciones además de infecciones por *Mycoplasma pneumoniae*. La aparición tardía de anticuerpos y la falta de especificidad y sensibilidad hacen que la prueba de aglutinina fría tengan poco valor.

Se han demostrado varios métodos para detectar anticuerpos en contra de *Mycoplasma* entre los que se encuentran la prueba de inhibición metabólica, una prueba de hemaglutinación y una prueba de fijación de complemento y una prueba de radioinmunoensayo. La prueba de fijación de com-

plemento es la que más comunmente utiliza en la práctica clínica. Un aumento de cuatro veces o mayor del título de fijación de complemento indica una infección reciente. Si solamente se obtiene un suero convalescente del paciente, un título de 1:64 mayor sugiere fuertemente una infección reciente.

La prueba de fluorescencia indirecta se ha utilizado para detectar anticuerpos en las secreciones bronquiales de pacientes con micoplasma neumonia. Esta técnica es rápida, sensitiva y específica. Solamente se encuentra en algunos centros.

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ENFERMEDADES ASOCIADAS AL SISTEMA DE HISTOCOMPATIBILIDAD HLA

Edwin Mejías, MD

Introducción

En los comienzos de este siglo diferentes estudios demostraron que ciertos tejidos de ratas y tumores podían transplantarse a animales de la misma variedad sin llevar a una reacción de rechazo por el huésped. Si esos tejidos eran transplantados a otras variedades o especies eran rechazados debido a factores tisulares específicos que eran reconocidos como extraños por el animal huésped. Los descubridores de estos factores les llamaron antígenos de histocompatibilidad. En el ratón se demostró que el control genético de estos factores tisulares estaba en el cromosoma 17 y se le llamó al sistema de histocompatibilidad en el ratón el complejo H-2. Esa información en animales experimentales ha servido de marco para entender mejor los antígenos de histocompatibilidad en humanos (1). Evidencia para un sistema similar en humanos surgió cuando se demostró que anticuerpos humanos reaccionaban con antígenos de la superficie celular que eran genéticamente controlados. Inicialmente se les llamó leucoaglutininas porque los anticuerpos se demostraron que reaccionaban con células blancas antigénicas extrañas en una forma parecida a la isohemaglutinina dirigida contra los antígenos ABO de células rojas. Hoy día, sabemos que estos antígenos genéticamente controlados se expresan no solo en células blancas sino que están en todas las células nucleadas del cuerpo. Estos antígenos se denominan HLA, queriendo de-

cir "Human Leukocyte Antigens". Es este grupo de antígenos el que se ha hecho de gran importancia en la tipificación de tejidos para transplantes de órganos y transfusión de células blancas.

Los genes del sistema HLA están localizados en un fragmento pequeño del sexto cromosomas (2, 3) y está comprendido por cuatro locus, A, B, C y D (Figura 1). Los antígenos HLA-A, B y C son unas glicoproteínas de 45,000 daltons que existen en la superficie celular en asociación a una beta₂-microglobulina, que es un polipéptido de 12,000 daltons cuya secuencia es homóloga con uno de los dominios de la región constante de la inmunoglobulina G (IgG) del humano (2). Estos antígenos se encuentran en todas las células nucleadas al igual que en plaquetas. La región HLA-D posee dos productos de genes: glicopéptidos de 34,000 y 29,000 daltons los cuales se combinan para formar una molécula de dos cadenas que está presente principalmente en la superficie de los linfocitos B, en algunos linfocitos T y macrófagos (1, 2).

A la derecha de la región HLA-D están los genes estructurales para los componentes segundo y cuarto de la cascada de complemento y para el factor B. Estos genes son moléculas grandes de muchas cadenas. Esta región se asume que codifica la secuencia de amino ácidos para todas las cadenas de estos componentes de complemento (2, 3).

El Sistema HLA y Asociación a Enfermedades

Aunque inicialmente tipificación para HLA se limitó a transplantes de órganos sabemos que hoy día puede ser aplicado fuera de ese cuadro. Por ejem-

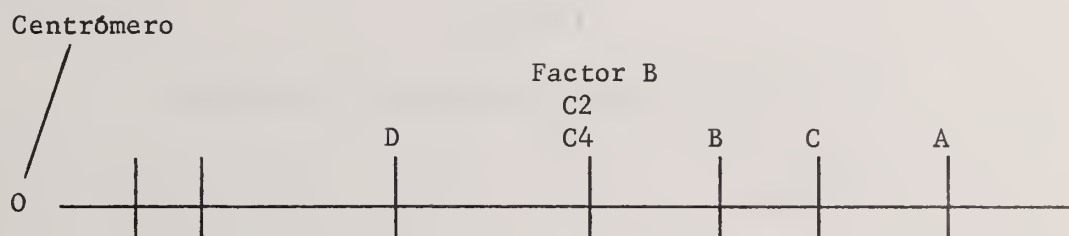


Figura 1: Genes del Complejo HLA

TABLA I

Enfermedades Reumáticas Asociadas al Sistema HLA

Enfermedad	Antígeno HLA
Espondiloartropatías Seronegativas	B27
Lupus Sistémico Eritematoso	B8
Vasculitis Cutánea	A11, BW35
Síndrome de Behcet	B5
Artritis Reumatoidea	DW4
Síndrome de Sjogrens	B8, DW3
Hemocromatosis	A3, B14

plo, se ha demostrado una asociación entre susceptibilidad a enfermedad y ciertos antígenos de este sistema en más de cuarenta enfermedades. En el 1973 se publicó la evidencia más fuerte entre un antígeno HLA en particular, HLA-B-27 y una enfermedad específica: espondilitis anquilosante (4, 5). Más interesante es el hecho de que entidades clínicamente relacionadas, como el síndrome de Reiters y espondilitis psoriática y llamadas colectivamente espondiloartropatías seronegativas también se asocian a este antígeno (6, 7) (Tabla I). Como vemos, en la

misma tabla, otras enfermedades reumáticas también se han asociado a otros tipos de HLA.

Además de la asociación del sistema HLA a ciertas enfermedades reumáticas se ha notado asociación con enfermedades de naturaleza autoinmune o de etiología desconocida (Tabla II). Interesante es la asociación de estas enfermedades autoinmunes con el locus HLA-D, como por ejemplo, artritis reumatoidea, hepatitis crónica activa y esclerosis múltiple. Es importante mencionar que la enfermedad se desarrolla en solo una minoría de los que poseen

TABLA II
Enfermedades Autoinmunes Asociadas al Sistema HLA

Enfermedad	Antígeno HLA
Enteropatía por Gluten	B8, DW3
Dermatitis Herpetiformis	B8, DW3
Psoriasis	B13, B17
Hepatitis Crónica Activa	B8, DW3
Myastenia Gravis	B8
Esclerorisis Múltiple	A3, B7, DW2
Diabetes Mellitus Juvenil	B8, BW15, DW3
Enfermedad de Adison	B8
Tirotoxicosis	B8

un alelo de susceptibilidad y finalmente que no todos los pacientes con una enfermedad en particular poseen el alelo asociado con susceptibilidad.

Aplicaciones Prácticas del Sistema HLA y Asociación a Enfermedades

La asociación particular de antígenos HLA con ciertas enfermedades tiene una variedad de implicaciones clínicas. Estas incluyen:

1. Clasificación de enfermedades
2. Diagnóstico
3. Pronóstico
4. Riesgo predictivo de desarrollar una enfermedad.

5. Consejo genético.
6. Consejo terapéutico.

Por ejemplo, la asociación entre HLA-B 27 y espondilitis seronegativas ha servido para clasificar ciertas enfermedades que antes se consideraban ser variantes de artritis reumatoidea. Se podría usar esas asociaciones por ejemplo en ayudar a diferenciar una enfermedad como en los casos de artritis gonocócica y el síndrome de Reiters. También podría ayudar en el diagnóstico temprano previo a cambios radiológicos o ser una clave que lleve a un diagnóstico posterior. Una aplicación importante sería en el caso de enfermedades asociadas a HLA en la cual la enfermedad se ha asociado a un miembro familiar, en tales casos tipificación para el feto podría establecer si el niño estará eventualmente a riesgo de desarrollar la enfermedad. Según avancen las investigaciones las implicaciones y aplicaciones prácticas

TABLA III

Características de Enfermedades Asociadas al Sistema HLA

-
1. Patofisiología Desconocida.
 2. Agente Etiológico Desconocido
 3. Tendencia Hereditaria
 4. Anormalidades Inmunológicas
 5. Cursos Sub-agudos o Crónicos
-

TABLA IV

Mecanismos de Enfermedades Asociadas al Sistema HLA

-
1. Genes de Respuesta y Supresión Inmune están ligadas al sistema HLA.
 2. Antígenos HLA Actúan como Receptores.
 3. Antígenos HLA Son Estructuralmente y Antigénicamente Similar a los Agentes Etiológicos.
 4. Antígenos HLA se incorporan a una cubierta viral.
 5. Defectos en mecanismos citotóxicos.
 6. Deficiencias en Componentes de Complemento.
-

de estas asociaciones nos ayudarán a entender un poco más el rol de la inmunogenética en desarrollar ciertas enfermedades.

Mecanismos de la Asociación entre HLA y Enfermedades

Estas asociaciones entre antígenos del siste-

ma HLA y enfermedades poseen ciertas características generales (Tabla III). La mayor parte de los mecanismos para explicar la asociación de HLA y enfermedad es aún desconocida, sin embargo se han postulado varias hipótesis (Tabla IV). La explicación para esas asociaciones es un campo para investigación futura la cual dependerá en un mejor conocimiento del origen de la enfermedad en cuestión. Se debe enfatizar que más de uno de esos mecanismos postulados podrían estar operando concurren-

temente para producir enfermedad y que diferentes mecanismos podrían aplicarse en asociaciones de enfermedades con distintos tipos de HLA. Se refiere a el lector a estudios publicados recientemente para un mejor entendimiento de esos posibles mecanismos (2, 3, 8).

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In Hypertension*...When You Need to Conserve K⁺

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

DYAZIDE®

ADD OR SUBSTITUTE
GUANETHIDINE

DYAZIDE®

ADD
VASODILATOR

DYAZIDE®

ADD BETA-BLOCKER, CNS
INHIBITOR OR RESERPINE

**EFFECTIVE STEP 1
DIURETIC THERAPY[†]** (when the
combination represents previously titrated dosage)

[†]Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K⁺ supplement or K⁺-sparing agent) and a maintenance phase (a diuretic alone or in combination with a K⁺ supplement or K⁺-sparing agent).

Serum K⁺ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards including fetal or neonatal jaundice, throm-

bocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K⁺ frequently, both can cause K⁺ retention and elevated serum K⁺. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Anti-hypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transiently elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with

possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

Supplied: Bottles of 1000 capsules, Single Unit Packages (unit-dose) of 100 (intended for institutional use only), in Patient-Pak™ unit-of-use bottles of 100.

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SK&F CO.
a SmithKline company
Carolina, P.R. 00630

Motrin[®] vs aspirin w/codeine...

(ibuprofen)



compare the analgesic effect

A *Motrin* 400 mg dose relieved postsurgical dental pain as effectively as a combination of 650 mg aspirin and 60 mg codeine (two aspirin-with-codeine No. 3 tablets) in a study of 129 patients.

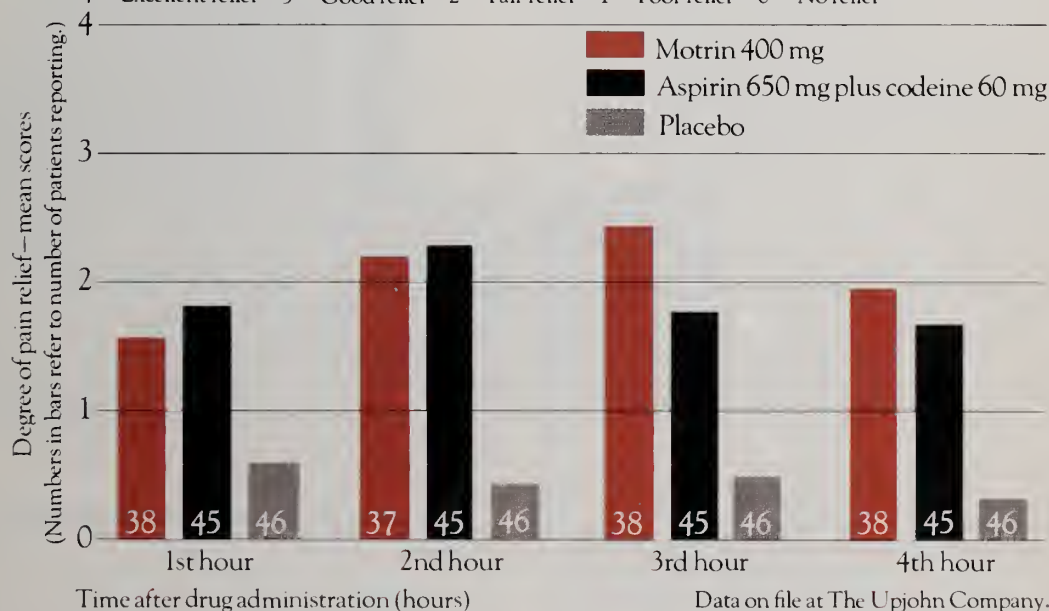
In this double-blind, placebo-controlled, randomized study, no statistically significant difference in relief of pain was noted at 1, 2, and 4 hours between the *Motrin* and aspirin-with-codeine groups... with *Motrin* being significantly more effective ($p = 0.03$) at the three-hour interval.

Active treatment was significantly more effective ($p < 0.0001$) than placebo at all time intervals.

Comparison of pain relief

Motrin vs aspirin-codeine combination

4 = Excellent relief 3 = Good relief 2 = Fair relief 1 = Poor relief 0 = No relief



One tablet q4-6h prn

For relief of mild to moderate pain:

Motrin[®] 400mg TABLETS
ibuprofen, Upjohn

- Not a narcotic • Not addictive • Not habit forming • Nonscheduled
- Acts peripherally • Relieves pain rapidly • Relieves inflammation • Indicated in acute and chronic pain • Well tolerated (The most common side effect with *Motrin* is mild gastrointestinal disturbance.)

Please turn the page for a brief summary of prescribing information.

Upjohn

Motrin® (ibuprofen) now proved an effective analgesic for mild to moderate pain

Motrin® Tablets (ibuprofen, Upjohn)

Indications and Usage: Relief of mild to moderate pain.

Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin:* Used concomitantly may decrease Motrin blood levels.

Coumarin: Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy nor by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness,* headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis, including flares of chronic disease: Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for relief of pain.

Do not exceed 2400 mg per day.

Caution: Federal law prohibits dispensing without prescription.

For additional product information, see your Upjohn representative or consult the package insert.

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

MED B-4-S

WHY I'M A UNITED WAY VOLUNTEER



STEPHEN GRAHAM

Home: Seattle, Washington

Career: Attorney

Age: 29

Married: One daughter

Interests: Hiking, writing, cartooning, bicycling and volunteering for United Way

"Because there's more to my life than just me.

"Like being with my family. Hiking along the timberline. And getting involved in my community.

"Volunteering for United Way adds another dimension to my life. I'm putting my skills to work for the benefit of the entire community. And I'm meeting all kinds of people who are doing the same.

"Most important of all, I'm learning more about human care needs. And how — as a United Way volunteer — I can make a difference here in Seattle. It's a valuable lesson in leadership.

"By helping shape my community's future, through United Way, I'm more than just living my life. I'm fulfilling it."



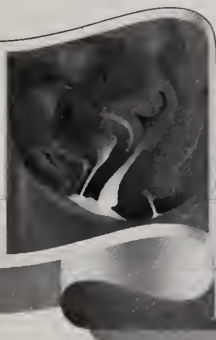
**Thanks to you...
it works...**

for ALL OF US United Way

BactrimTM (trimethoprim and sulfamethoxazole) succeeds

Bactrim is useful for the following infections when due to susceptible strains of indicated organisms (see indications section in summary of product information):

Expanding its usefulness in antimicrobial therapy



in recurrent UTI...
a continuing record of high clinical effectiveness against common uropathogens

in acute otitis media in children...
effective against both major otic pathogens...with b.i.d. convenience

in acute exacerbations of chronic bronchitis in adults...
clears the sputum and lowers its volume...on b.i.d. dosage

in shigellosis...
faster relief of diarrhea than with ampicillin²

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morgani*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. Note: The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. Limited clinical information presently available on effectiveness of treatment of otitis media with Bactrim when infection is due to ampicillin-resistant *Haemophilus influenzae*. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS.

Clinical studies show that patients with group A β -hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: General: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. **Blood dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. **Allergic reactions:** Erythema

multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. **Gastrointestinal reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. **CNS reactions:** Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. **Miscellaneous reactions:** Drug fever, chills, toxic nephrosis with oliguria and anuria, periarthritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:

Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS:

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: Double Strength (DS) tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose[®] packages of 100; Prescription Paks of 20 and 28. Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose[®] packages of 100; Prescription Paks of 40. Pediatric Suspension, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry-flavored—bottles of 100 ml and 16 oz (1 pint). Suspension, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).



ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

BactrimTM succeeds

in recurrent urinary tract infections*

from site to source

Bactrim continues to demonstrate high clinical effectiveness in recurrent urinary tract infections. Bactrim reaches effective levels in urine, serum, and renal tissue¹...the trimethoprim component diffuses into vaginal secretions in bactericidal concentrations¹... and in the fecal flora, Bactrim effectively suppresses Enterobacteriaceae^{1,2} with little resulting emergence of resistant organisms.

1. Rubin RH, Swartz MN: *N Engl J Med* 303:426-432, Aug 21, 1980. 2. Data on file, Medical Department, Hoffmann-La Roche Inc.

maximizes results with B.I.D. convenience

BactrimTM DS

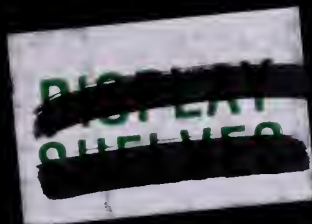
160 mg trimethoprim and 800 mg sulfamethoxazole

DOUBLE STRENGTH TABLETS



* due to susceptible strains of indicated organisms

Please see previous page for summary of product information.



BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

CONTENIDO:

EDITORIAL — CASOS DE ELECTROCARDIOGRAFIA PEDIATRICA

EL SISTEMA DE COMPLEMENTO: FUNCIONES BIOLOGICAS

EL SISTEMA DE COMPLEMENTO: DEFICIENCIAS PRIMARIAS

NEVOID BASAL CELL CARCINOMA SYNDROME

EXPERIENCE WITH RENAL CYST ASPIRATION

THE PREVALENCE OF THERMOPHILIC ACTINOMYCETES IN SUGAR CANE
RELATED ENVIRONMENTS AND PRECIPITINS IN THE POPULATION
IN PUERTO RICO

FORO DE MEDICINA NUCLEAR: REITER'S SYNDROME

CASOS DE ELECTROCARDIOGRAFIA PEDIATRICA

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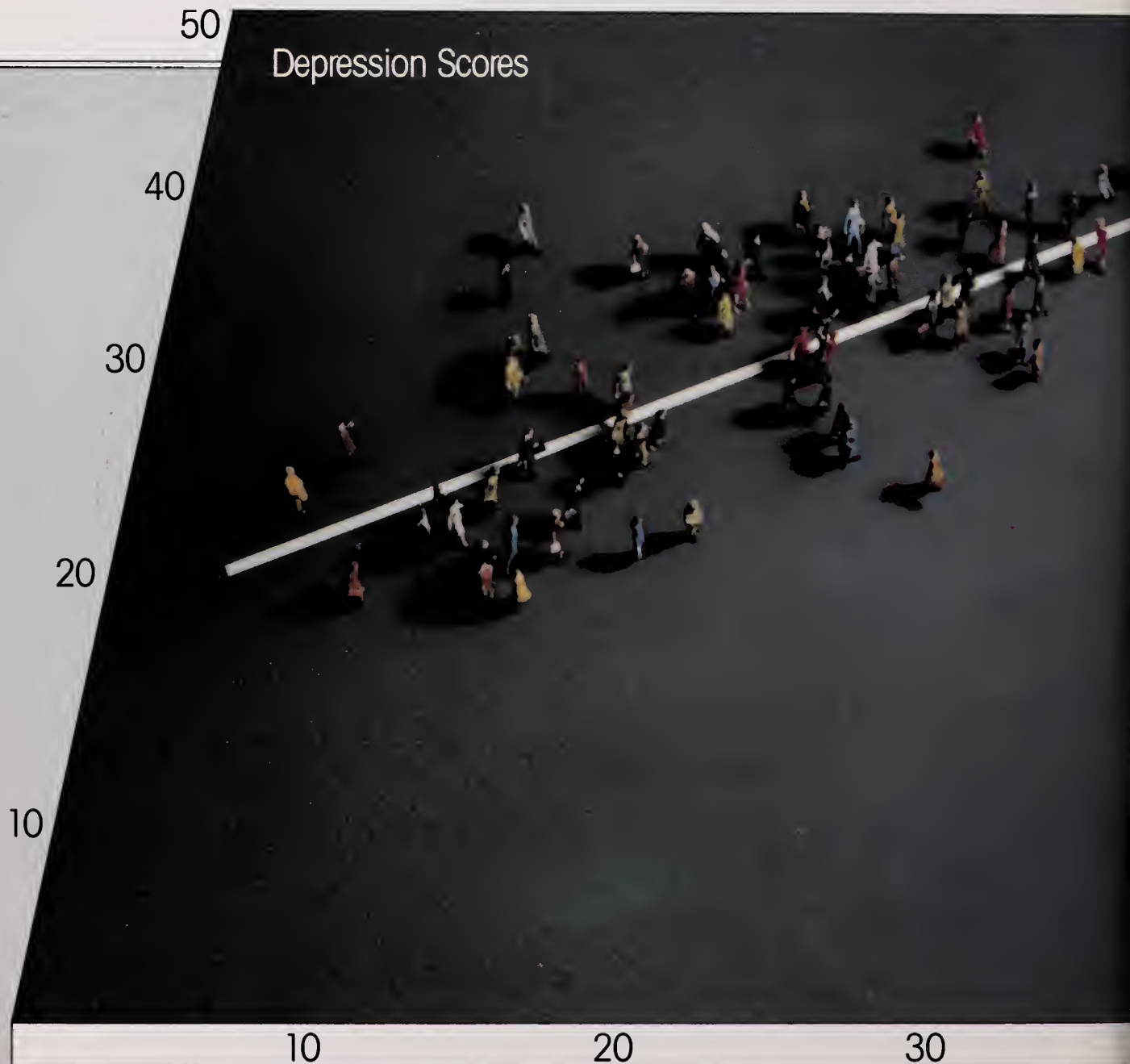
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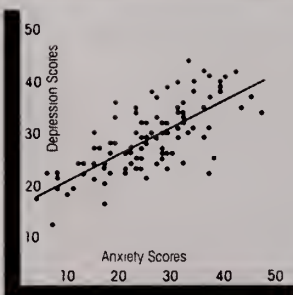
FOR THE 7 OF 10 NONPSYCHOTIC



Clear correlation between anxiety and depression³

The above graph illustrates a relationship between anxiety and depression, indicating that patients seldom present with anxiety or depression alone; more often they have both in varying degrees. Data based on a sampling of 100 outpatients (64 male; 36 female) seen at a general psychiatric clinic.

³Adapted from Claghorn, J. The anxiety-depression syndrome. *Psychosomatics* 11:438-441, Sept-Oct 1970.



DEPRESSED PATIENTS WHO ARE ALSO ANXIOUS^{1,2}

Most depressed patients are also anxious. . .

Some authors estimate that 70% of all nonpsychotic patients with symptoms of depression have concomitant symptoms of anxiety.^{1,2} One author found a distinct correlation between anxiety and depression scores in 100 nonpsychotic outpatients administered the Minnesota Multiphasic Personality Inventory in a general psychiatric clinic.³ As depression scores increased, so did anxiety scores. No attempt was made to select patients other than to exclude psychotics.

but not psychotic

The logic of treating both components of anxious depression is clear. Antipsychotics, like the phenothiazines, however, carry a well-documented risk of tardive dyskinesia.⁴ Because of this, an APA Task Force recently recommended the judicious use of phenothiazines in cases other than chronic psychosis or the use of alternative treatments.

A better way to give relief

Limbitrol combines the specific anxiolytic action of Librium® (chlordiazepoxide HCl/Roche)—a benzodiazepine with a long history of safe use—with the antidepressant action of amitriptyline, a tricyclic of established clinical efficacy. In comparison to phenothiazines, Limbitrol and its components have rarely been associated with tardive dyskinesia or other extrapyramidal side effects. And in terms of rapid response and patient compliance, Limbitrol appears to be superior to amitriptyline alone. Controlled multiclinic studies showed Limbitrol relieved more symptoms more rapidly than did amitriptyline.⁵ Despite a higher incidence of drowsiness, the dropout rate due to side effects was lower with Limbitrol. (See adverse reactions section in summary of product information on next page. As with any CNS-acting agent, patients should be cautioned about driving or using dangerous machines while on therapy with Limbitrol.)

References: 1. Rickels K: Drug treatment of anxiety, in *Psychopharmacology in the Practice of Medicine*, ed. Jarvik ME. New York, Appleton-Century-Crofts, 1977, p. 316. 2. Schatzberg AF, Cole JO: Benzodiazepines in depressive disorders. *Arch Gen Psychiatry* 35:1359-1365, 1978. 3. Claghorn J: The anxiety-depression syndrome. *Psychosomatics* 11:438-441, 1970. 4. The Task Force on Late Neurological Effects of Antipsychotic Drugs: Tardive dyskinesia, summary of a task force report of the American Psychiatric Association. *Am J Psychiatry* 137:1163-1172, 1980. 5. Feighner JP *et al*: A placebo-controlled multicenter trial of Limbitrol versus its components (amitriptyline and chlordiazepoxide) in the symptomatic treatment of depressive illness. *Psychopharmacology* 61:217-225, 1979.

Anxiety Scores

50

In moderate depression and anxiety

Limbitrol®

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Relief without a phenothiazine

Please see summary of product information on next page.

LIMBITROL® TABLETS Tranquilizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses). Myocardial infarction and stroke reported with use of this class of drugs. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated. Sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12.

In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. IV administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly. Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10. Prescription Packs of 50.



Lung cancer is now an equal opportunity tragedy.

Remember when lung cancer was a man's disease. Because men had been smoking longer than women. But the women's smoking boom that started in the 1930's and 40's—is paying most cruel dividends today. Yet most people still think lung cancer is a man's disease. Tell your female patients the true story. That lung cancer is now an equal opportunity tragedy. That's what "you've come a long way, baby" is all about.

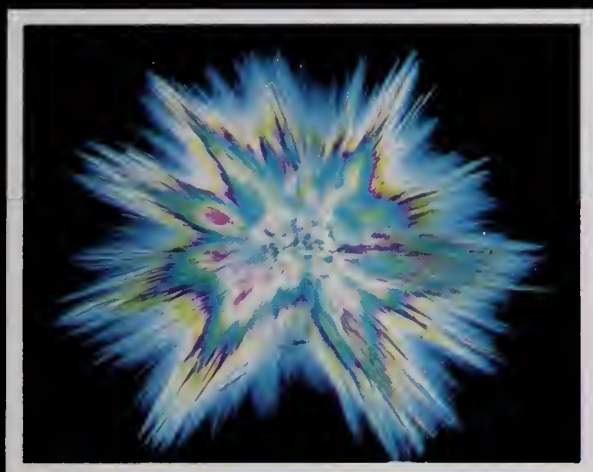
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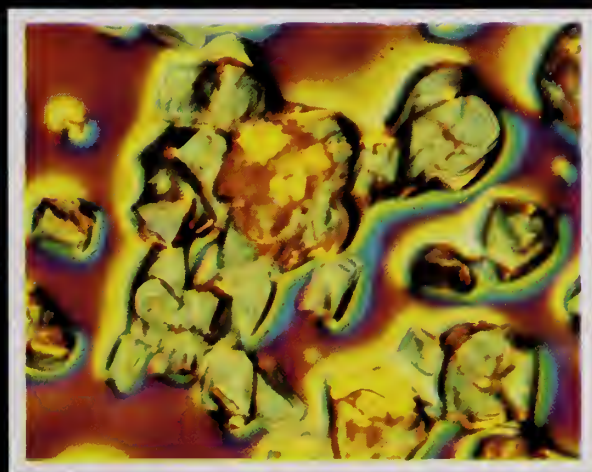
U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Office on Smoking and Health
Public Health Service Rockville, MD 28057

THE BASICS

BEHIND A NEW
EFFECTIVE THERAPY FOR
HYPERTENSION



Prazosin crystal hydrated for purposes of photomicrographic illustration.



Polythiazide crystal hydrated for purposes of photomicrographic illustration.

INTRODUCING...

NEW Minizide® 

PRAZOSIN HCl/POLYTHIAZIDE

Capsules containing prazosin HCl equivalent to 1 mg, 2 mg or 5 mg prazosin plus 0.5 mg polythiazide.

**COMBINES TWO BASIC
EFFECTIVE CONTROL**



**REDUCED
PERIPHERAL VASCULAR
RESISTANCE
WITH MINIPRESS®
(PRAZOSIN HCl)**



PRINCIPLES FOR THE OF HYPERTENSION

Prazosin and polythiazide crystals hydrated
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PLASMA VOLUME
WITH AN
EFFECTIVE THIAZIDE

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PRAZOSIN HCl/POLYTHIAZIDE

Capsules containing prazosin HCl equivalent to 1 mg, 2 mg or 5 mg; prazosin plus 0.5 mg polythiazide



COMBINES TWO BASIC PRINCIPLES FOR THE EFFECTIVE CONTROL OF HYPERTENSION

BRIEF SUMMARY

MINIZIDE® CAPSULES (prazosin hydrochloride/polythiazide) FOR ORAL ADMINISTRATION

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dose so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

INDICATIONS AND USAGE. MINIZIDE is indicated in the treatment of hypertension (See box warning.)

CONTRAINDICATIONS. RENESE (polythiazide) is contraindicated in patients with anuria, and in patients known to be sensitive to thiazides or to other sulfonamide derivatives.

WARNINGS. MINIPRESS (prazosin hydrochloride): MINIPRESS may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy.

RENESE (polythiazide): RENESE should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Thiazides may be additive or potentiative of the action of other antihypertensive drugs.

Potential occurs with ganglionic or peripheral adrenergic blocking drugs.

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medications such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop with thiazides as with any

potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate the metabolic effects of hypokalemia, especially with reference to myocardial activity.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in hepatic or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be either increased, decreased, or unchanged. Latent diabetes mellitus may become manifest during thiazide administration.

Thiazide drugs may increase responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazides may decrease serum protein-bound iodine levels without signs of thyroid disturbance.

PRECAUTIONS. Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic or mutagenic studies have been conducted with MINIZIDE. However, no carcinogenic potential was demonstrated in 18 month studies in rats with either MINIPRESS or RENESE at dose levels more than 100 times the usual maximum human doses. MINIPRESS was not mutagenic in *in vivo* genetic toxicology studies.

MINIZIDE produced no impairment of fertility in male or female rats at 50 and 25 mg/kg/day of MINIPRESS and RENESE respectively. In chronic studies (one year or more) of MINIPRESS in rats and dogs, testicular changes consisting of atrophy and necrosis occurred at 25 mg/kg/day (60 times the usual maximum recommended human dose). No testicular changes were seen in rats or dogs at 10 mg/kg/day (24 times the usual maximum recommended human dose). In view of the testicular changes observed in animals, 105 patients on long term MINIPRESS therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on MINIPRESS alone for up to 51 months did not have changes in sperm morphology suggestive of drug effect.

Use in Pregnancy: Pregnancy Category C. MINIZIDE was not teratogenic in either rats or rabbits when administered in oral doses more than 100 times the usual maximum human dose. Studies in rats indicated that the combination of RENESE (40 times the usual maximum recommended human dose) and MINIPRESS (8 times the usual maximum recommended human dose) caused a greater number of stillbirths, a more prolonged gestation, and a decreased survival of pups to weaning than that caused by MINIPRESS alone. There are no adequate and well-controlled studies in pregnant women. Therefore, MINIZIDE should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether MINIPRESS or RENESE are excreted in human milk. Thiazides appear in breast milk. Thus, if use of the drug is deemed essential the patient should stop nursing.

Pediatric Use: Safety and effectiveness in children has not been established.

ADVERSE REACTIONS. MINIPRESS (prazosin hydrochloride): The most common reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS, some of them rarely (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular: edema, dyspnea, syncope, tachycardia.
Central Nervous System: nervousness, vertigo, depression, paresthesia.
Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.
EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.
Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopy studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

RENESE (polythiazide): Gastrointestinal: anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.

Central Nervous System: dizziness, vertigo, paresthesia, headache, xanthopsia.
Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.
Dermatologic: purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis).
Cardiovascular: orthostatic hypotension may occur and be aggravated by alcohol, barbiturates or narcotics.
Other: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness.

OVERDOSAGE. MINIPRESS (prazosin hydrochloride): Accidental ingestion of at least 50 mg of MINIPRESS in a two year old child resulted in profound drowsiness and depressed reflexes. No decrease in blood pressure was noted. Recovery was uneventful.

Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate that MINIPRESS is not dialyzable because it is protein bound.

RENESE (polythiazide): Should overdosage with RENESE occur, electrolyte balance and adequate hydration should be maintained. Gastric lavage is recommended, followed by supportive treatment. Where necessary this may include intravenous dextrose and saline with potassium and other electrolyte therapy, administered with caution as indicated by laboratory testing at appropriate intervals.

DOSAGE AND ADMINISTRATION. MINIZIDE (prazosin hydrochloride/polythiazide): Dosage as determined by individual titration of MINIPRESS (prazosin hydrochloride) and RENESE (polythiazide) (See box warning.)

Usual MINIZIDE dosage is one capsule two or three times daily the strength depending upon individual requirement following titration.

The following is a general guide to the administration of the individual components of MINIZIDE.

MINIPRESS (prazosin hydrochloride): Initial Dose: 1 mg two or three times a day (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

RENESE (polythiazide): The usual dose of RENESE for antihypertensive therapy is 2 to 4 mg daily.

HOW SUPPLIED.

STRENGTH	COMPONENTS	COLOR	CAPSULE CODE	PKG. SIZE
MINIZIDE 1	1 mg prazosin - 0.5 mg polythiazide	Blue/Green	430	100's
MINIZIDE 2	2 mg prazosin - 0.5 mg polythiazide	Blue/Green/Pink	432	100's
MINIZIDE 5	5 mg prazosin - 0.5 mg polythiazide	Blue/Green/Blue	436	100's



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PFIZER INC.

BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

(USPS-060000)

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Examine Me.

During the past several years, I have heard my name mentioned in movies, on television and radio talk shows, and even at Senate subcommittee sessions. And I have seen it repeatedly in newspapers, magazines, and yes, best-sellers. Lately, whenever I see or hear the phrases "overmedicated society," "overuse," "misuse," and "abuse," my name is one of the reference points. Sometimes even *the* reference point.

These current issues, involving patient compliance or dependency-proneness, should be given careful scrutiny, for they may impede my overall therapeutic usefulness. As you know, a problem almost always involves improper usage. When I am prescribed and taken correctly, I can produce the effective relief for which I am intended.

Amid all this controversy, I ask you to reflect on and re-examine my merits. Think back on the patients in your practice who have been helped through your clinical counseling and prudent prescriptions for me. Consider your patients with heart problems, G.I. problems, and interpersonal problems who, when their anxiety was severe, have been able to benefit from the medication choice you've made. Recall how often you've heard, as a result, "Doctor, I don't know what I would have done without your help."

You and I can feel proud of what we've done together to reduce excessive anxiety and thus help patients to cope more successfully.

If you examine and evaluate me in the light of your own experience, you'll come away with a confirmation of your knowledge that I *am* a safe and effective drug when prescribed judiciously and used wisely.

For a brief summary of product information on Valium (diazepam/Roche)® , please see the following page. Valium is available as 2-mg, 5-mg and 10-mg scored tablets.

Valium® diazepam/Roche

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal, adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy). The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindications: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Use in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other anti-depressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

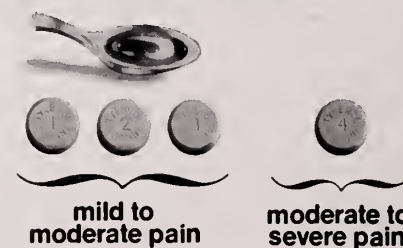
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. **Adults:** Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed, adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d., adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions). **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam/Roche) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10. Prescription Paks of 50, available in trays of 10.

TYLENOL® with Codeine

tablets & elixir



Summary of Prescribing Information

Description

Tablets: Contain codeine phosphate*: No. 1—7.5 mg. (¼ gr.); No. 2—15 mg. (½ gr.); No. 3—30 mg. (¾ gr.); No. 4—60 mg. (1 gr.)—plus acetaminophen 300 mg.

Elixir: Each 5 ml. contains 12 mg. codeine phosphate* plus 120 mg. acetaminophen (alcohol 7%).

*Warning: may be habit forming

Actions: Acetaminophen is an analgesic and antipyretic; codeine an analgesic and antitussive.

Contraindications: Hypersensitivity to acetaminophen or codeine.

Warnings: *Drug dependence:* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to other oral narcotics. Subject to the Federal Controlled Substances Act.

Use in ambulatory patients: Caution patients that codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with this drug may exhibit additive CNS depression. When such a combination is contemplated, reduce the dose of one or both agents.

Use in pregnancy: Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Pediatric use: Safe dosage of this combination has not been established in children below the age of three.

Precautions: *Head injury and increased intracranial pressure:* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: Codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients: Administer with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: Most frequent: lightheadedness, dizziness, sedation, nausea and vomiting, more prominent in ambulatory than nonambulatory patients; some of these reactions may be alleviated if the patient lies down. Others: euphoria, dysphoria, constipation and pruritus.

Dosage and Administration: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. **TYLENOL with Codeine tablets** are given orally. The usual adult dose is: Tablets No. 1, No. 2, and No. 3: One or two tablets every four hours as required. Tablets No. 4: One tablet every four hours as required. **TYLENOL with Codeine elixir** is given orally. The usual doses are **Children (3 to 6 years):** 1 teaspoonful (5 ml.) 3 or 4 times daily; **(7 to 12 years):** 2 teaspoonful (10 ml.) 3 or 4 times daily; **(under 3 years):** safe dosage has not been established. **Adults:** 1 tablespoonful (15 ml.) every 4 hours as needed.

Drug Interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings.

For information on symptoms/treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing.

TYLENOL with Codeine tablets are manufactured by McNeil Laboratories Co., Dorado, Puerto Rico 00646.

Caution. Federal law prohibits dispensing without prescription.

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Potent pain relief without aspirin complications



TYLENOL[®] with Codeine

tablets  / elixir 

Tablets Contain acetaminophen 300 mg plus codeine phosphate* as follows:
No.1—7.5 mg (1/8 gr); No.2—15 mg (1/4 gr); No.3—30 mg (1/2 gr); No.4—60 mg (1 gr)
Elixir Each 5 ml contains 12 mg codeine phosphate* plus 120 mg acetaminophen (Alcohol 7%)

*Warning: May be habit forming

α

Alpha Stimulation

Central Control of
Blood Pressure*



*The Family of Man" by Roberto Moretti,
a statuery in crystal symbolizing the broad range of
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The Alpha Advantage:

It's for all kinds of hypertensives

- Unlike beta blockers, Catapres® has no contraindications.
- Catapres can be useful even in these patients with:

Congestive heart failure	Allergic rhinitis
Ventricular hypertrophy	Hepatic disease
Hyperglycemia	Hyperuricemia
Diabetes mellitus	Gouty arthritis
Bronchial asthma	Sulfonamide hypersensitivity

Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

work/play—normal hemodynamic responses to exercise maintained.

love—low incidence of impotence and/or loss of libido:
2.8% in 1,923 patients studied.¹

cardiac output—tends to return to control values during long-term therapy.

blood flow—preserved in kidney.

No Single Advantage Determines Drug Choice.

Other factors must include:

The drug's effectiveness in a given patient, its side effects, warnings, precautions, tolerance, etc. A rational therapeutic choice depends on a careful assessment of all such factors.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

¹ Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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0.3 mg tablets**

Tablets of 0.1, 0.2, 0.3 mg
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(clonidine HCl)
Hypertension

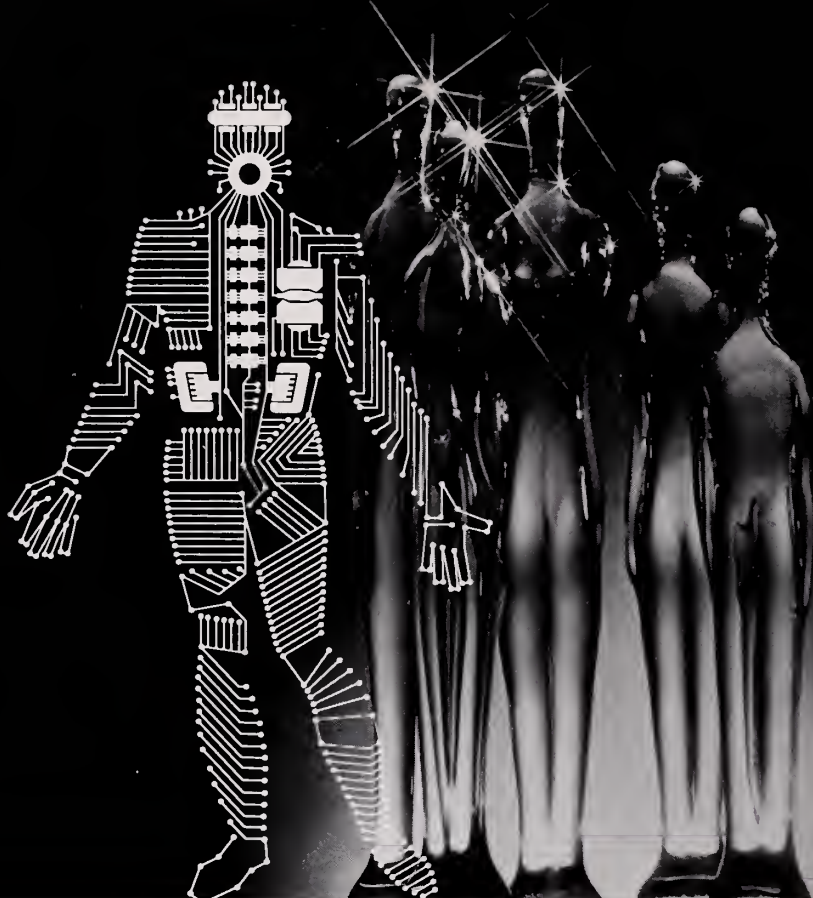




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Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

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Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

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Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of

The usual starting dose of Catapres is 0.1 mg at breakfast and 0.1 mg at bedtime. Some patients may benefit from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg
Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chloralhydrate and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000. Also available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

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CASOS DE ELECTROCARDIOGRAFIA PEDIATRICA

El objetivo de hacerle un electrocardiograma a un niño es obtener información que junto con el historial, el examen físico, y los hallazgos radiográficos nos puedan ayudar a reconocer algún trastorno cardíaco específico.

El electrocardiograma es de particular importancia diagnóstica en el caso de las arritmias, las cuales suelen estar presentes luego de cirugía cardíaca, en miocardiopatías, hipoxia, desbalance electrolítico, y aún en niños normales. El electrocardiograma es el medio con el cual logramos hacer el diagnóstico definitivo de estas arritmias que hasta hace poco se decía: "en Pediatría son raras, pocas veces diagnosticadas, y casi nunca tratadas" (1). En la práctica diaria de la Cardiología Pediátrica hemos podido comprobar que esa aseveración no es correcta, pues son frecuentes, el Pediatra logra identificarlas la mayoría de las veces, y las que así lo requieren reciben el tratamiento antiarrítmico indicado.

El Boletín de la Asociación Médica de Puerto Rico, con la intención de compartir esa experiencia y contribuir al mejoramiento educacional de sus lectores ha añadido una nueva sección: los Casos de Electrocardiografía Pediátrica. El objetivo de la misma es familiarizar al Pediatra y Médico Generalista con algunos hallazgos electrocardiográficos en niños, la mayoría de ellos recogidos en pacientes asintomáticos referidos para consulta.

Los casos serán presentados en forma de "quiz" con varias alternativas diagnósticas para escoger la más adecuada. La discusión será concisa y con un enfoque práctico.

Aquellos con poca experiencia en electrocardiografía de niños deben tener en mente que las variantes normales son más frecuentes que el adulto; y que la etiología, el enfoque terapéutico y el pronóstico también son muchas veces diferentes para la misma condición en el niño que en el adulto.

Si recordamos la frase que tantas veces nos repitieron en nuestros años de formación pediátrica: "los niños son diferentes", veremos que la electrocardiografía no es una excepción.

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EL SISTEMA DE COMPLEMENTO: DEFICIENCIAS PRIMARIAS

María L. Santaella, MD

Summary: An actualized review is presented on the Complement System, emphasizing its biological properties.

The most relevant literature on the subject is discussed.

Resumen: Se presenta un repaso actualizado del Sistema de Complemento, enfatizando sus funciones biológicas.

En el mismo se ha considerado la literatura más relevante sobre el tema.

La literatura médica disponible a generalistas, especialistas en Medicina Interna y sub-especialistas hace referencia continuamente al sistema de complemento.

Reconociendo la importancia que tiene el mismo para explicar fenómenos biológicos y entidades clínicas, se presenta esta serie de dos artículos. En el primero de estos se define el sistema y se exponen las funciones biológicas del mismo; en el segundo, se discuten las deficiencias primarias de las proteínas que componen este sistema.

El sistema de complemento se estudió por primera vez a comienzos de este siglo, cuando se hizo evidente que el suero humano fresco contenía una serie de factores que podían mediar el proceso de lisis de bacterias al igual que el proceso de lisis de células sensibilizadas por anticuerpo (1, 2). Concurrentemente surgió una metodología que permitió el análisis de los componentes de este sistema por métodos bioquímicos (3).

Consta de una serie de más de veinte pro-

teínas en suero, activadas en secuencia, como resultado de lo cual surgen diversos fenómenos biológicos. Sus funciones primordiales son: mediar aspectos del proceso de inflamación; facilitar la ingestión de patógenos por células fagocíticas (lo que se conoce como el proceso de opsonización); solubilización de complejos inmunes (4) y destrucción de bacterias o bacteriolisis (5-7).

Normalmente las proteínas de este sistema circulan en forma de precursores inactivos en la circulación y constituyen aproximadamente el 15 por ciento por peso de la fracción de las globulinas en el plasma.

Se conoce muy poco de la función del complemento en individuos normales y de los factores que regulan el nivel de cualquiera de los componentes. La razón de circulación de estas proteínas es relativamente rápida; en la mayor parte de los casos de 1-2 por ciento por hora (8).

En términos de síntesis, hay evidencia de producción de estas proteínas desde la quinta semana de gestación (9). Al nacer, los niveles de los distintos componentes son de 50-75 por ciento de los de la madre (a excepción de C8 y C9 que son el 10 por ciento) y para el tercer a sexto mes de vida alcanzan los niveles del adulto. Al presente se cree que el material genético que se traduce en la síntesis de los componentes C2, C4, C6, C8 y factor B está dentro o próximo al complejo de histocompatibilidad mayor en el cromosoma número seis.

Las proteínas de este sistema se producen en diversas células (10-12). Alrededor del 90 por ciento de C3, C6, C8 y el factor B se sintetiza en el hígado; C1 se produce en células epiteliales del intestino y C2, C4, C5 y C8 en macrófagos.

Nomenclatura del Sistema

Los componentes del sistema se designan por letras mayúsculas y números: C1, C2, etcéte-

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TABLA I
Mecanismos de Activación del Sistema de Complemento

	Vía Clásica	Vía Alternativa
Inmunológicos	IgG, IgM Complejos Inmunes	IgA, IgG, IgE
No-inmunológicos	DNA Proteína C reactiva Proteína A del estafilococo Enzimas parecidas a tripsina	Endotoxina Materiales de contraste Membranas de celofán de equipos de diálisis Equipo de circulación extracorporea Enzimas parecidas a tripsina

ra. Algunos componentes tienen nombres específicos como properdina, y otros se designan con letras, factor B, factor D.

Cada componente es activado en secuencia bajo ciertas condiciones apropiadas, generándose enzimas a lo largo del proceso de activación. Estas enzimas se designan con una barra sobre el símbolo de los componentes que las constituyen: $\overline{C42}$, $\overline{C3bBb}$.

Los fragmentos que resultan de la acción enzimática se designan por letras minúsculas después del símbolo del componente: C4a, C4b.

Activación de las Vías

Se han descrito dos vías: la clásica y la alternativa. La activación (iniciación) de estas vías puede ser por mecanismos inmunológicos o por mecanismos no-inmunológicos.

En la Tabla I se incluyen estos mecanismos.

En el caso de la vía clásica, una molécula de IgM puede iniciarla; por el contrario, se necesitan dos moléculas de IgG juntas para comenzar la cascada. Solamente IgG1, IgG2 y la IgG3 pueden activar la vía clásica y de las tres, IgG3 es la más eficiente (13).

Recientemente se han recalcado distintos mecanismos no-inmunológicos que inician la vía alternativa. Se ha encontrado que cuando el plasma entra en contacto con la membrana de ciertos aparatos de diálisis, hay activación de complemento que lleva a leucopenia (14). Los leucocitos, predominantemente neutrófilos y monocitos, son secuestrados en el pulmón. Aunque transitoria, esta leucostasis puede ser dañina, sobre todo si ocurre frecuentemente (15, 16). Este fenómeno también se ha descrito respecto a la activación de esta vía por las fibras de nilón utilizadas en equipo de leucaféresis (17, 18).

La infusión de material radiográfico de contraste se asocia con reacciones tipo alérgicas en aproximadamente un 5 por ciento de todos los pacientes.

Hoy se interpretan estas reacciones anafilactoideas (ya que no son mediadas por IgE) como el resultado de la generación de fragmentos de complemento (C3a y C5a) que tienen actividad de anafilotoxinas (19, 20). Debe recalcar que el material usado para hacer el colestograma oral puede tener el mismo efecto.

Finalmente, en un estudio de 15 pacientes sometidos a cirugía con la utilización de circulación extracorpórea, se concluye que la producción de C3a y C5a pueda contribuir a la patogénesis de los síndromes post bomba (21).

Vía Clásica

Como se señala anteriormente, esta vía puede ser iniciada por diversos mecanismos. Si se toma como ejemplo la IgG, dos moléculas de la misma se localizan una al lado de la otra sobre la superficie celular reconociendo las determinantes antigénicas que tiene la célula. A través de una región en la molécula de inmunoglobulina, conocida como el dominio CH2, el anticuerpo se entrelaza con el primer componente de complemento, C1. Este primer componente es una macromolécula compuesta de tres subunidades que se designan como C1q, C1r y C1s, las cuales se mantienen unidas en presencia de calcio (22). La porción de C1q es la que se une al anticuerpo.

Al unirse C1q al anticuerpo, se activa C1r, que a su vez activa C1s, generando actividad de esterasa. C1s viene en contacto con C4, el próximo componente, el cual es dividido en dos fragmentos: C4b, que se queda pegado a la superficie celular y C4a, que se desprende al medio. La combinación de C4b en la membrana celular, cerca del C1 activado, activa a C2, que a su vez se divide en dos fragmentos, C2a (que permanece unido a C4b) y C2b (que se desliga).

El C4 y el C2 combinados constituyen una enzima proteolítica (C4b2a) llamada también convertasa de C3, ya que divide al C3 en dos fragmentos: C3a y C3b. Este último fragmento unido al complejo C4b2a en la membrana celular forma una enzima nueva capaz de actuar sobre C5. C5 también se divide en dos fragmentos, C5a y C5b. El C5b

queda unido a la membrana y atrae al C6 y C7 para formar el complejo C5b67. Finalmente C8 y C9 se unen al complejo C5b67 para que se produzca un "hueco funcional" en la membrana celular. La célula pierde la capacidad de mantener el equilibrio osmótico al introducirse esta secuencia terminal de proteínas (C5 a C9), hay movimiento de iones y agua, y finalmente ocurre lisis (23-25).

Vía Alterna

La vía alterna de complemento, conocida anteriormente como el sistema de properdina (del Latín "perder", que quiere decir destruir), se reconoció inicialmente como la ruta de activación de complemento independiente de anticuerpo. Sin embargo, hoy se sabe que también puede ser activada por IgG, IgM, IgA e IgE.

Esta secuencia se inicia cuando los factores B y D interaccionan con C3, generándose el complejo $\overline{\text{C3bBb}}$ que tiene actividad enzimática, capaz de dividir C5 y continuar la secuencia igual que la vía clásica (26). El complejo $\overline{\text{C3bBb}}$ a su vez puede dividir más C3, y tiene acción enzimática lábil. La función de properdina es estabilizar la enzima $\overline{\text{C3bBb}}$.

Al hablar de la vía alterna debe hacerse un paréntesis para mencionar el factor C3 nefrítico (C3 NeF). Originalmente descrito en pacientes con glomerulonefritis crónica hipocomplementémica (27) y luego en pacientes con lipodistrofia parcial (28), hoy se conoce la naturaleza de este factor. El factor C3NeF es una inmunoglobulina del tipo IgG que funciona uniéndose a la convertasa de la vía alterna ($\overline{\text{C3bBb}}$), creándose un complejo trimolecular estable que imposibilita la disociación de la enzima (29). Por lo tanto, la presencia de esta inmunoglobulina perpetúa la activación de la vía alterna y consume complemento (30).

Por último se debe señalar un aspecto importante en términos de la función de esta vía en los mecanismos de control de infecciones. Se sabe que los activadores naturales de la vía alterna carecen o tienen relativamente poco ácido siálico (un constituyente de las glicoproteínas y los glicolípidos de algunas membranas). La mayor parte de las bacte-

TABLA II
Actividades Biológicas del Complemento

Función Biológica	Componentes
Aumenta la asociación de complejos de antígeno-anticuerpo	C1
Neutralización de virus	C4b (35, 36)
Actividad parecida a la de quinina	Fragmento de C2
Factor quimiotáctico; anafilotoxina	C3a (37)
Factor quimiotáctico; anafilotoxina	C5a (37)
Opsonina; activación de la vía alterna; inicia la descarga de complejos de antígeno-anticuerpo de la superficie de leucocitos	C3b
Adherencia via receptores en linfocitos y macrófagos	C3d
Mobilización de leucocitos de la médula ósea a la periferia	C3e (38)
Factor quimiotáctico	C5b67
Daño lento a la membrana	C8
Daño rápido a la membrana	C9

rias carecen de ácido siálico (31).

Mecanismos de Control del Sistema

Por razones obvias, el sistema de complemento no puede permanecer activado continuamente. Para regular su activación existen una serie de mecanismos entre los cuales se mencionan los siguientes:

Inhibidor de la actividad de esterasa de C1-

una proteína que inhibe la activación de C1 combinándose con C1s, deteniendo así la vía clásica (32).

Inactivador de C3b - una enzima que ataca C3b en solución o en superficies celulares, dividiendo el fragmento C3b en C3c y C3d con la ayuda de β 1H y una enzima parecida a tripsina. Al dividirse C3b, se pierde la actividad de las convertasas (38).

β 1H - una proteína que acelera la acción del inactivador de C3b (33).

Labilidad de las convertasas $\overline{C42}$ y $\overline{C3bBb}$;

TABLA III

Significado de Niveles Anormales de Complemento

Alteración	Significado
CH50 bajo o cero	Considerar deficiencia primaria
C4 y C3 bajo: factor B normal	Considerar activación de la vía clásica
Factor B y C3 bajo; C4 normal	Considerar activación de la vía alterna
CH50 alto	Considerar proceso infeccioso

TABLA IV

Condiciones Asociadas con Niveles Altos de Complemento

Ictericia obstructiva
Tiroiditis
Fiebre reumática aguda
Artritis reumatoidea
Poliarteritis nodosa
Dermatomiositis
Infarto agudo del miocardio
Colitis ulcerosa
Fiebre tifoidea
Diabetes mellitus
Gota
Síndrome de Reiter's

labilidad de C5b y C5b67.

Inactivadores de las anafilotoxinas C3a y C5a - enzimas que destruyen las actividades biológicas de estos fragmentos.

Actividades Biológicas del Complemento

En la Tabla II, se indican las funciones de

los componentes y de los fragmentos que resultan a lo largo de la activación de estas vías.

Debe recalcar que el fragmento C3b (producto de C3, el componente donde convergen ambas vías) es la opsonina por excelencia de este sistema. Opsonización es el proceso mediante el cual un organismo o célula es cubierto por un factor (como C3b) para acelerar el proceso de fagocitosis.

De la tabla debemos definir el término de

TABLA V

Condiciones Asociadas con Niveles Bajos de Complemento

Lupus eritematoso sistémico con glomerulonefritis
Glomerulonefritis aguda; glomerulonefritis membranoproliferativa
Enfermedades de complejos inmunes
Cirrosis hepática
Crioglobulinemia mixta
Endocarditis infecciosa con glomerulonefritis
Malnutrición

quimiotaxis. Este significa la migración de células dirigidas al área de inflamación por un estímulo químico (como C3a, C5a y C5b67).

elevación y depresión de los niveles de complemento respectivamente.

Determinación y Significado de los Niveles de Complemento

Al presente hay métodos para medir los nueve componentes de la vía clásica, la mayoría de los componentes de la vía alterna, y varias de las enzimas e inhibidores que regulan el sistema de complemento (34).

Por la necesidad de ser breve, no se detallan los métodos disponibles. En general, hay dos tipos de técnicas: aquellas que miden los componentes como antígenos en suero (usando la técnica de inmunodifusión radial sencilla) y aquellas que miden la actividad funcional de los componentes (usando un sistema de lisis de células sensibilizadas con anticuerpo). Se denomina CH50 a la prueba que mide la actividad hemolítica total de complemento, y esta es la primera que debe ordenarse para evaluar la función de este sistema.

En la Tabla III se incluye el significado de estas pruebas, y en las Tablas IV y V se mencionan algunas de las entidades clínicas caracterizadas por

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New evidence is in: Treatment of mild hypertension can save lives

Even among patients with DBP in the low 90s, systematic therapy significantly reduced mortality:

■ Of nearly 11,000 hypertensives identified by the Hypertension Detection and Follow-up Program, slightly more than 70% had mild hypertension (DBP 90-104 mm. Hg).¹

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BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance, namely hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and

related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily. **How Supplied:** Tablets—100 mg (white, scored), 50 mg (aquea) in bottles of 100, 1000 and 5000; 25 mg (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

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* Persistent extrapyramidal symptoms may require discontinuation of the use of the drug.

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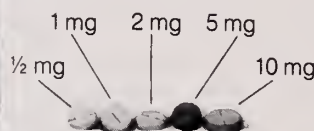
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Warnings: Usage in Pregnancy: Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards. Infants should not be nursed during drug treatment.

Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity.

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur), (2) receiving anticonvulsant medication since HALDOL haloperidol may lower the convulsive threshold, (3) with known allergies or a history of allergic reactions to drugs. Concomitant antiparkinson medication, if required, may have to be continued after HALDOL haloperidol is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time. The 1, 5, 10 mg tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Adverse Reactions: CNS Effects: Extrapyramidal Reactions. Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn.

Persistent Tardive Dyskinesia: Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by reinstitution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms.

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice reported. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia and hypoglycemia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other neuroleptic drugs.

The injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

Caution: Federal law prohibits dispensing without prescription.

1892

IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

HALDOL tablets and concentrate (120 ml) are manufactured by McNeil Pharmaceutical Co., Dorado, PR 00646.

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EL SISTEMA DE COMPLEMENTO: DEFICIENCIAS PRIMARIAS

María L. Santaella, MD

Summary: A review is presented on the Genetic Complement Deficiencies, emphasizing important aspects of the topic discussed in the most recent literature.

Resumen: Se presenta un repaso de Las Deficiencias Genéticas del Sistema de Complemento, enfatizando aspectos sobresalientes del tema discutidos en la literatura más reciente.

En este artículo repasamos las deficiencias primarias de las proteínas que componen el sistema de complemento y de sus proteínas de control. No se discuten las condiciones en las cuales se encuentra bajo el complemento por haber una entidad clínica subyacente.

Las deficiencias genéticas del sistema de complemento son condiciones raras. Se han descrito defectos de todos los constituyentes de la vía clásica (1, 2); defectos combinados que envuelven algunos componentes de la vía alterna (3); y deficiencias de algunas de las proteínas que controlan la cascada de complemento, deficiencia del inhibidor de C1 (4) y deficiencia del inactivador de C3b (5, 6).

Estos estados de deficiencias usualmente resultan de la herencia de genes cuyos productos no se detectan o no son funcionales. Los individuos que son homocigóticos para estos genes que no producen la proteína tienen un CH50 de cero. Los heterocigóticos tienen aproximadamente la mitad del nivel normal. Este patrón de herencia se conoce co-

mo autosómica co-dominante (7). La presentación clínica es generalmente la del tipo autosómico recesivo, debido a que el heterocigótico no tiene manifestaciones clínicas usualmente.

Las entidades clínicas a discutirse pueden ser divididas en tres grupos de acuerdo a las situaciones clínicas. La ausencia de componentes tempranos de la vía clásica se asocia a un aumento en la incidencia de condiciones de autoinmunidad; deficiencia de C3 o de su inactivador resulta en un aumento en susceptibilidad a infecciones bacterianas (semejando a las deficiencias de anticuerpos); y las deficiencias de los factores terminales que conllevan una mayor incidencia de infecciones por organismos del grupo de Neisseria.

Deficiencia de C1q

Se ha reportado deficiencia de C1q en pacientes con hipogamaglobulinemia ligada al cromosoma X y con inmunodeficiencia severa combinada (8). Sin embargo, en estos casos se ha demostrado un aumento en el catabolismo de C1q que se cree pueda ser secundario a los niveles bajos de inmunoglobulina (9). Esta deficiencia se ha descrito también en casos de síndromes parecidos a lupus eritematoso sistémico con susceptibilidad aumentada a infecciones bacterianas (10).

Se ha llamado síndrome hipocomplementémico con vasculitis y urticaria al cuadro clínico asociado a urticaria persistente, angitis leucocástica, angioedema severo, artritis, artralgias, anormalidades neurológicas e hipocomplementemia. Las anormalidades de complemento son las siguientes: C1q bajo; C1r y C1s normal; C4, C2 y C3 bajo y C5 a C9 normal (11). La presencia de precipitinas del tipo C1q de bajo peso molecular se ha descrito en estos casos. Entre las posibles explicaciones de la natu-

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raleza de estas precipitinas se encuentran las siguientes: que representan IgG anti-C1q; que son complejos inmunes pequeños; que representan una reacción de precipitación del tipo no-inmunológico y que constituyen una gama globulina que se enlaza a C1q independientemente de una interacción de antígeno-anticuerpo (12).

Deficiencia de C1r y C1s

Se han descrito varios casos de deficiencia de C1r y de C1s. Las manifestaciones clínicas son parecidas a lupus eritematoso con una mayor susceptibilidad a infecciones bacterianas (13-17).

Deficiencia de C4

La deficiencia de C4 se ha descrito en individuos totalmente asintomáticos. También se ha asociado a lupus eritematoso sistémico, presentándose en forma atípica en uno de los casos debido a que las pruebas inmunológicas eran negativas (ANA, preparación L. E. e inmunoglobulinas en piel (18, 19).

Deficiencia de C2

De los estados de deficiencia de complemento primaria, la deficiencia de C2 es la más común (se estima que 1 en 10,000). Alrededor de la mitad de los pacientes con deficiencia de C2 que se han descrito tienen lupus eritematoso o un desorden relacionado (7). En los grupos de pacientes estudiados, se encuentra una tendencia a tener el inicio de la enfermedad a una edad más temprana, a tener envolvimiento renal leve y a haber títulos más bajos de ANA (20).

Entre las otras entidades que se han descrito en asociación con la deficiencia de C2 están las siguientes: púrpura anafilactoidea, dermatomiositis y lupus discoide. También se ha descrito una susceptibilidad aumentada a infecciones.

La asociación de esta deficiencia con las entidades de autoinmunidad se ha explicado a base de

varias teorías. Primeramente, se ha demostrado que el complemento está envuelto en la solubilización de complejos inmunes (21), y por lo tanto un defecto en complemento podría alterar la disposición de los complejos. En segundo lugar, se ha sugerido un posible origen viral para lupus, y el complemento participa en la neutralización viral. Por último, la relación entre los genes que codifican para C2, C4 y el factor B con el complejo de histocompatibilidad mayor dentro del cual residen los genes de la respuesta inmune debe mencionarse.

Deficiencia de C3

Se han descrito varios casos de deficiencia de C3 en forma homocigótica (22, 23). En estos casos se reportan infecciones severas recurrentes por bacterias encapsuladas. Estudios *in vitro* demuestran generación deficiente de factores quimiotácticos y opsonización anormal de bacterias. *In vivo*, estos pacientes no responden con la leucocitosis que normalmente se espera durante procesos infecciosos. El heterocigótico no tiene manifestaciones clínicas ni demuestra tener mayor susceptibilidad a infecciones.

Deficiencia y disfunción de C5

La deficiencia de C5 ha sido estudiada en dos familias numerosas (24-26). El caso índice se presentó con lupus eritematoso sistémico con enfermedad renal leve e infecciones frecuentes. La media hermana de este paciente tenía 1-2 por ciento de los niveles normales de C5, y no había enfermedad concomitante presente excepto por infecciones del tracto respiratorio alto y dos episodios de pulmonía por pneumococo. Estudios *in vitro* han demostrado actividad hemolítica y bactericida disminuida, al igual que baja producción de factores quimiotácticos. Debe señalarse que la deficiencia de C5 es compatible con ausencia de manifestaciones clínicas.

Disfunción de C5 es lo que se conoce como el síndrome de Leiner's, caracterizado por dermatitis severa, inhabilidad para crecer e infecciones repetidas con una variedad de bacterias Gram-negativas

y estafilococos. In vitro, estos pacientes tienen disminución en la capacidad de opsonización de levaduras (27) y su nivel antigénico de C5 es normal. Varios casos han mejorado de las infecciones al dárseles plasma fresco.

Deficiencias de los componentes terminales (C6, C7, C8 y C9)

Los pacientes con deficiencia homocigótica de C6, C7 y C8 demuestran una susceptibilidad aumentada a infecciones con *Neisseria* diseminadas (28-32). Las infecciones reportadas han sido meningitis por meningococo y artritis gonocócica.

En cuanto a deficiencia de C7, se han reportado con las siguientes entidades clínicas: fenómeno de Raynaud's, esclerodactilia, telangiectasia, espondilitis anquilosante y lupus eritematoso. Respecto a este último, es interesante señalar que al repasar la literatura se encuentra que la incidencia de lupus eritematoso sistémico está aumentada en pacientes con deficiencias de los componentes terminales (7 por ciento comparada con 0.05 por ciento en la población general (33)).

Además de asociarse infecciones con *Neisseria* por deficiencia cuantitativa de C8, se ha descrito un caso de deficiencia funcional de C8 con infecciones recurrentes por meningococo (34).

El caso descrito en la literatura de deficiencia de C9 es de un paciente masculino de 76 años de edad con enfermedad de arterias coronarias, aneurisma de la aorta abdominal y osteoartritis (35). El paciente demostró tener un CH50 de 30 por ciento de lo normal; niveles antigénicos de C9 no-detectables y lisis de eritrocitos al igual que actividad bacteriana mediada por complemento procediendo a una razón más lenta.

Deficiencias combinadas

Se ha descrito deficiencia de C2 con deficiencia parcial de factor B (3), presentándose con septicemias recurrentes por pneumococo.

Lachmann et al (36) reportan un caso de

deficiencia combinada de C6 y C7 sin enfermedades concomitantes.

Por último, se han informado casos de deficiencia de C2 con deficiencia de IgG1 y con inmunodeficiencia común variable (37).

Deficiencia y disfunción del inhibidor de C1

La deficiencia del inhibidor de la acción de esterasa de C1 se ha asociado a lupus eritematoso, a lupus discoide y al angioedema hereditario.

El angioedema hereditario se caracteriza por episodios de edema en las extremidades, la cara, el tronco, las vías respiratorias y el tracto gastrointestinal, los cuales ocurren espontáneamente o secundarios a trauma (38, 39). Este edema no es depresible, es indoloro y no es prurítico.

La condición se hereda de forma autosómica dominante y afecta igualmente ambos sexos. Se han descrito dos formas desde el punto de vista del defecto envuelto: la forma común que constituye el 85 por ciento de los casos, y la forma variante que ocurre en un 15 por ciento de los casos. La primera surge de haber una baja concentración del inhibidor de C1; la segunda ocurre por tener un inhibidor en concentraciones adecuadas pero sin ser funcional.

El diagnóstico se hace por el cuadro clínico y las pruebas de laboratorio, las cuales demuestran nivel bajo de C4, C3 normal y nivel bajo del inhibidor pero sin tener actividad funcional.

El tratamiento del angioedema hereditario ha sido ampliamente discutido en la literatura (38, 40, 41).

Deficiencia del inactivador de C3b

Se han informado dos pacientes con deficiencia del inactivador de C3b (5, 6). Los pacientes descritos tienen mayor susceptibilidad a infecciones bacterianas. El perfil de complemento revela niveles bajos de C3 y factor B, debido a que el inactivador no está regulando la vía alterna (que está encendida continuamente).

Tratamiento de las deficiencias primarias de complemento

En el caso de co-existir una deficiencia de complemento y una condición del tipo de las enfermedades autoinmunes, el tratamiento será el de la condición primaria.

En ciertos casos de infecciones severas con deficiencias concomitantes, el uso de plasma fresco y el reemplazo de la proteína ausente ha sido de utilidad.

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NEVOID BASAL CELL CARCINOMA SYNDROME

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Abstract: The autosomal dominant inherited nevoid basal cell carcinoma syndrome is characterized by multiple basal cell carcinomas, multiple jaw cysts, skeletal abnormalities, pitting of palms or soles and calcification of falx cerebri. Three cases are reported and the literature is reviewed.

Abstracto: El síndrome de carcinomas basocelulares nevoides, heredado en forma autosomal dominante, se caracteriza por la presencia de carcinomas basocelulares múltiples, quistes mandibulares múltiples, anomalías esqueléticas, hoyuelos en palmas y plantas y calcificaciones del falx cerebri. Estamos reportando tres casos e incluyendo un repaso de la literatura.

Introduction

The basal cell nevus syndrome or Gorlin-Goltz syndrome is a well recognized condition described by Howell and Caro in 1959, and by Gorlin and Goltz in 1960. This is an autosomal dominant inherited disease characterized by multiple basal cell carcinomas of the skin, epidermal cysts of the jaws and cyst, palmar-plantar pits and other multiple malformations.

The purpose of this paper is to present three cases of this condition, the first Puerto Rican ones ever reported as far as we know.

Case No. 1

This is a 67-year-old caucasian, Puerto Rican who

was seen for the first time at the dermatology clinic of the University District Hospital on March 1976 due to multiple brownish lesions which were appearing on face since about six years prior to that date. At that time, the patient was found to have multiple palmar pits, multiple basal cell carcinomas on face, accessory tragus on right preauricular area, a below-average intelligence, a negative skull series, a negative chest plate, and a negative skeletal survey.

One of the patient's brother who lives in New York suffers of jaw cyst. No other member of his family according to patient have the same condition as him.

On 1951, the patient was operated due to intestinal polyposis. On 1960, an hemorrhoidectomy, and on 1968, a transurethral resection of the prostate for benign prostate hypertrophy were done. He has been operated, too, for chalazion on right eye and hydrocele on right testicle. A lipoma was excised from left axillae on 1978.

The physical examination showed multiple (about 30) pigmented lesions with central depression and raised pearl borders, sizes varying from 1 to 4mm, located on face, predominantly on left periorbital region (Fig. 1) and on right temporal scalp.

On right preauricular area, he had two accessory tragus (Fig. 2). The inferior one measured 2.5 cm length x 1 cm width, while the superior one measured 0.5 length x 1 cm width.

On the neck, back and face, the patient had multiple flat scars from previous treated lesions. On palms and soles, multiple tiny (1-2 mm) pits were seen (Fig. 3).

Except for Kyphoscoliosis, the rest of the physical examination was unremarkable.

Since 1976 on, he has been treated by multiple (about 30) biopsies followed by curettage and electrodesiccation for the basal cell carcinomas on face and neck areas.

Case No. 2

This is a 50-year-old male caucasian, Puerto Ri-



Figure 1: Case No. 1. Note the multiple pigmented papules with central depression and raised pearly borders on left periorbital region.

can male who was referred to the dermatology clinic of the University District Hospital on 1964 by a private dermatologist with a diagnosis of Basal Cell Nevoid Syndrome. He had been followed by this physician for several years due to the appearance of multiple basal cell carcinoma on face since the age of 20. He was operated, too, by a private surgeon of a lipoma on hand prior to 1964.

The patient had no other major diseases. He came from a family of four siblings, neither of whom have the condition. According to patient, his dead-father suffered of multiple "moles" on his face, similar to the ones he has.

The skull series showed multiple radioluscent areas in the mandible and maxilla with many impacted teeth. He was referred to the dental surgery service where he had been operated several times since 1964 for extraction of impacted teeth, and curettage, enucleation and marsupialization of dental cysts.

At the dermatology clinic, he has undergone multiple (about 25-30) biopsies followed by electrodesiccation and curettage, cryotherapy, or radiotherapy for basal cell carcinomas on face, neck and back.

The physical examination of the patient showed multiple (about 25) pigmented pearly papules sized from 1 to 3 mm (Fig. 4). Several of them have central depression. They were located mainly on the right cheek and right periorbital region. They were also present on forehead, neck and back. Multiple scars were found on previously treated



Figure 2: Case No. 1. Accessory tragi on right preauricular area.

areas.

Multiple reddish, tiny (1-2 mm) pits were found on palms and soles.

Located on the right foot toes, four firm, 0.5 cm x 0.5 cm, flesh-colored firm papules were found, one on the second toe, two on the third toe and one on the fourth toe (Fig. 5). On the left thumb and the second left finger, there were a 1.5 cm x 1 cm firm nodule on the volar aspect, and a 0.5 cm x 0.5 cm firm papule on the lateral aspect, respectively (Fig. 6).

He had a right-sided thoracic scoliosis of the spine. Rest of the physical examination was unremarkable.

Case No. 3

This is a 65-year-old white, Puerto Rican female



Figure 3: Case No. 1. Palmar pits.



Figure 5: Case No. 2. Flesh colored papules on right foot toes.

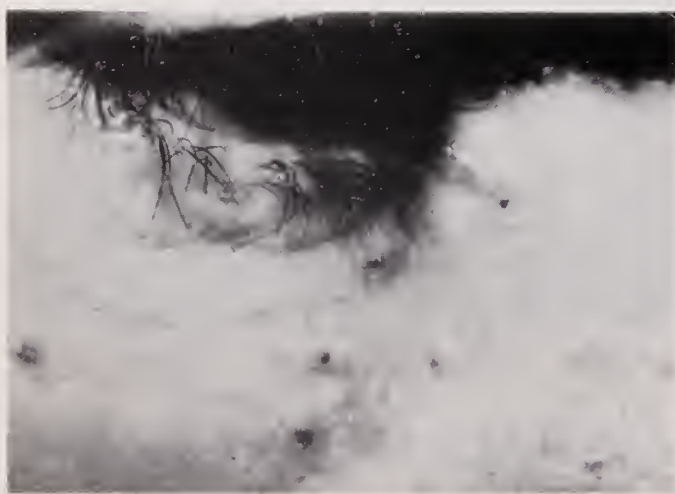


Figure 4: Case No. 2. Multiple pearly papules with central depression on right periorbital region.



Figure 6: Case No. 2. Flesh colored nodules on left hand (arrows).

seen for the first time at University District Hospital (U. D. H.) dermatology clinic on 1968 due to a 40-year-history of progressive appearance of multiple dark spots on face and body. These began as flat macules and, later on, become elevated and shiny, and tended to increase in size very slowly. By that time, she noted, too, the appearance of multiple palmar pits. She was treated by private dermatologists prior to 1968.

At the dermatology clinic, the patient underwent multiple (about 10-15) biopsies followed by curettage and

electrodessication, or radiotherapy for basal cell carcinomas on head, neck, and back.

On June 1969, October 1970, April 1972 and June 1974, respectively, a Gardner's cyst of the left ovary and leiomyoma of the uterus, an epidermoid cyst on left hand, an epidermoid cyst on the left angle of mouth, and a chalazion on right eye were excised. She was treated for syphilis with penicillin on 1958. There was no history of any other major diseases. Nobody in her family had the same condition as far as she recalled.

The physical examination disclosed a well developed, obese female patient who had multiple pearly pigmented papules. Several of them had ulcerated and crusted center and were located on face, predominantly around the eyes and the nose. The patient had, too, multiple scars on previously treated and operated sites of head, neck and back. Located on both palms, there were multiple tiny (1-2 mm) pits. The rest of the physical examination was otherwise unremarkable.

A skull series done to the patient showed a small sella turcica and hyperostosis frontalis interna. No jaw cysts or defective dentition were found. A chest plate was negative.

The patient was subsequently lost for further follow up on 1978.

Histologic Features

The histologic examination of the lesions of all three patients were similar showing buds and nests of basaloid cells with peripheral palisading. They were diagnosed as basal cell carcinomas. A biopsy of the nodule of the left thumb of case No. 2 was diagnosed as epidermoid cyst.

Comments

Howell and Caro (1959) (1), and Gorlin and Goltz (1960) (2) recognized the existence of a distinctive familial syndrome consisting of multiple basal cell epitheliomas, jaw cysts and bifid ribs. Many cases have since been reported with associated abnormalities affecting nearly every system of the body. In the past many cases were confused with epithelioma adenoides cysticum (multiple trichoepitheliomas) (3).

The nevoid basal cell carcinoma (NBCC) syndrome is believed to be of autosomal dominance inheritance with marked penetration and variable expressivity (4). In some patients with the syndrome, the incidence of spontaneous chromosomal breakage tends to be increased (5). Males and females are equally affected. The syndrome is predominantly seen in caucasians, but few cases in negroes have been reported (6). Possible association with

the Gardner's syndrome have been suggested (7).

The major characteristic findings (8) of the NBCC syndrome are: multiple basal cell carcinomas on exposed and unexposed areas occurring at an early age, multiple benign jaw cysts, skeletal anomalies, pitting of the palms and soles, and calcification of the falx cerebri. Due to variations in expressivity in a given case or family, one or more of these major components may be minimal or absent (6). Sporadic cases are known to occur (4, 6, 9). The diagnosis can be firmly established if the patient has at least nevi or cysts combined with either a calcified falx or pits (10). All of our patients have the nevi and the pits.

Fifty percent of the patients have multiple nevoid lesions which may appear at birth, but are more common from puberty to 35 years of age (11). They could occur later in life, too. A single patient may have from a few lesions to many thousands. They are usually reddish-brown to flesh colored and of varying size. The lesions are predominantly on face and neck but no area of the body is spared. They may appear in crops or may arise continually. They tend to grow rapidly for a few days or weeks and, thereafter, the majority tend to remain static for variable periods. The nevi may show invasion, usually after the first decade (8, 11). These nevi arise from the basal cells of the epidermis and not from melanocytes. The lesions should be treated as ordinary basal cell carcinomas with curettage and dessication, cryosurgery, simple excision, Mohs chemosurgery, topical 5-fluoracil, or radiotherapy. Metastasis have been reported (12).

Fifty to sixty percent of patients with the NBCC syndrome exhibit multiple pitting of palms or soles (13). They are small (1-3 mm) red hollows on palms or soles which are believed to be areas of dyskeratosis from which the central plug has fallen out (10). Histologically, under the light microscope, the pits have shown thinning of the stratum granulosum, vacuolization of the stratum malphigii, and irregular shape and size of the rete ridges at the base of the pit. Under the electron microscope, they have shown poorly developed tonofibrils, small keratohyaline granules, incompletely discharged cementsomes, and premature desquamation of the hor-

ny cells (14, 15, 16). It has been hypothesized that the epidermis underlying the pits have several similarities to the cells of basal cell epitheliomas and represent a basal cell epithelioma in situ (14, 16). The occasional formation of basal cell carcinoma from these pits, although rare, lend support to this hypothesis.

The jaw cysts are quite common in the syndrome and are seen with roentgenograms. They are multiple, unilocular, and of size varying from microscopic to several centimeters. They may occur as early as six years of age, but the average age of onset is about 13 years (13). The mandible is involved twice as frequently as the maxilla. They are mostly located in the premolar and molar regions of the mandible and in the second molar region of the maxilla (13). The first signs of the jaw cysts may be a bulging jaw or spontaneous fracture, although, usually they are asymptomatic. Infection and loosening of teeth may eventually supervene. Histologically, they are odontogenic keratocysts lined by squamous epithelium that usually features variable degree of keratinization. Microcysts may be present. The cysts spread through the cancellous bone first and only later involve in the cortex, so extensive replacement of the jaw may occur (10). The lesions are very difficult to treat, and less than radical excision is usually followed by a high rate of recurrence (10), possibly from adjacent microcysts or daughter cysts. Malignant sarcomatous degeneration has occurred as a result of radiotherapy to the cyst.

Lamellar calcification of the dura and the falx cerebri occur more commonly in these patients than in the population at large (13).

Skeletal abnormalities are present in up to 75 percent of the patients (11). Among the most common ones are the rib abnormalities (such as bifid ribs, synostosis, partial agenesis and cervical rudimentary ribs), frontal and parietal bossing, broad nasal root, ocular hypertelorism, mild mandibular prognathism, well developed supraorbital ridges, shortened fourth and fifth metacarpals, kyphoscoliosis and bridging of the sella turcica. Less common ones are pectus excavatum, pes planus, hallux valgus, defective clavicle, cervical and thoracic vertebral fusion, high arched palate, radioluscent deformities of the parietal bone and microcephaly.

Nearly every organ may be affected in the NBCC syndrome. Other cutaneous abnormalities include epidermoid cysts, lipomas, milia, hyperhidrosis, acrocyanosis, telangiectasia, multiple fibroepithelial polyps of the tongue, ash-leaf hypopigmentation and ichthyosis. It is the first time, as far as we know, that supernumerary tragi have been reported.

Ophthalmologic abnormalities include congenital blindness due to cataracts, chalazions, internal strabismus, coloboma of the choroid and optic nerve, glaucoma, corneal leukoma, medulated nerve fibers and epicanthal folds. Central nervous system abnormalities includes agenesis of corpus callosum, medulloblastoma, congenital hydrocephalus, EEG changes, mental retardation, schizophrenia and meningioma. Soft tissue abnormalities includes lymphatic mesenteric cyst, ovarian fibromas and cysts, multiple uterine fibromas, malrotation of bowel, inguinal hernia and kidney malformations. Reproductive system abnormalities include hypogonadism and undescended testes in males. Endocrine system abnormalities include diabetes mellitus, and hyporesponsive pseudohypoparathyroidism. This last finding is still under discussion (17).

Conclusion

We have presented three cases which fill the main criterias for nevoid basal cell carcinoma syndrome, the first Puerto Rican ones to our best knowledge.

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EXPERIENCE WITH RENAL CYST ASPIRATION

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Abstract: The increased use of intravenous pyelography as a screening procedure has revealed an increasing number of asymptomatic renal masses.

Surgical exploration has been the traditional approach for definitive evaluation of these masses. The availability of newer diagnostic techniques allow differentiation of benign and malignant masses by non-surgical means.

We propose a systematic approach for evaluation of asymptomatic renal masses which reduces the morbidity and mortality to patients as well as being more cost effective than the traditional surgical approach.

Our experience with this protocol since 1978 is presented.

Resumen: Al utilizar el pielograma intravenoso (IVP) como procedimiento rutinario en la evaluación del paciente, se ha encontrado un aumento en el número de masas renales asintomáticas. Hasta el momento, el manejo de estas lesiones renales había sido la exploración quirúrgica.

Con las nuevas técnicas de diagnóstico por imágenes se puede diferenciar entre lesiones malignas o no-malignas.

A continuación se propone un manejo sistemático para la evaluación diagnóstica de masas renales asintomáticas, con el cual se reduce la morbi-

lidad y mortalidad de los pacientes, y el costo médico envuelto en dicho proceso.

Nuestra experiencia con este protocolo, desde el 1978, es presentada.

The increased use of intravenous pyelography as a screening procedure has revealed an increasing number of asymptomatic renal lesions. Asymptomatic renal masses were diagnosed in 4.6 percent of all patients undergoing urography (98/2, 146) and 0.4 percent of all patients admitted to a general hospital (104/23, 631) (1).

Benign cystic lesions accounted for at least three quarters of these masses (1). Benign renal cysts have been reported in 3.5 percent of autopsy material (1). Coexistence of cysts and hypernephroma within the lesion has been reported in 10 of 1007 cases reviewed (2, 3).

Surgical exploration has been the traditional approach for the evaluation of all renal masses. A mortality of 1.6 percent to 3 percent and a morbidity of 30 percent has been reported in exploration of cysts that ultimately proved to be benign (4). Surgical morbidity and mortality increase with age, as does the incidence of benign renal cysts.

There are multiple diagnostic procedures that when used in combination allow differentiation of benign and malignant renal masses with 98-100 percent accuracy (1, 5, 15). Among these are nephrotomography, sonography and arteriography. Renal cyst puncture with biochemical and histological analysis of aspirate has proven highly reliable to evaluate neoplasms and has been adopted by many ins-

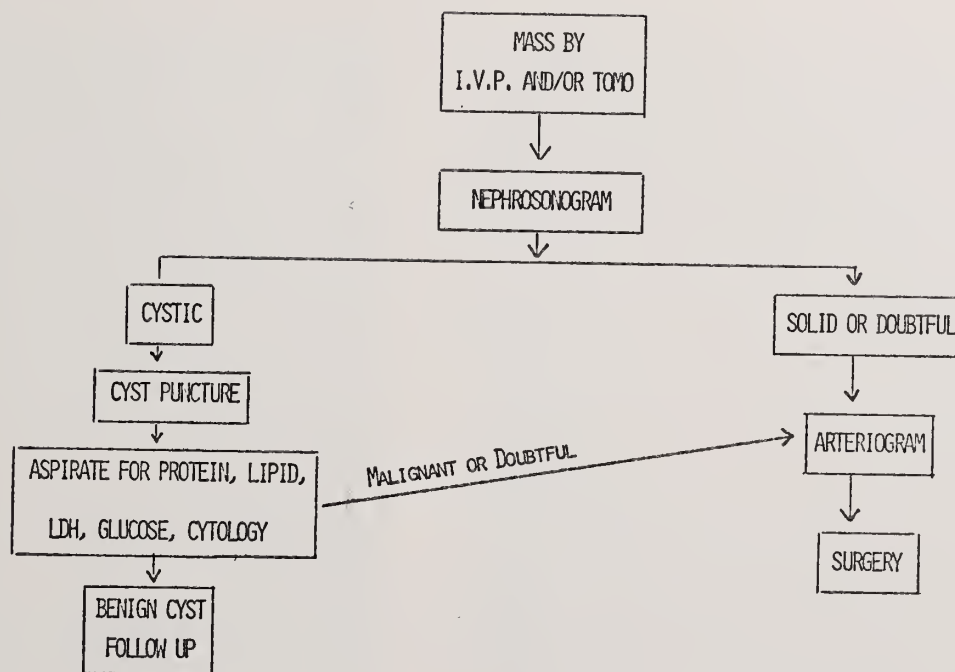


Figure 1: Protocol for Renal Mass Evaluation

tifications with no renal tumors misdiagnosed as cysts (5, 6, 13, 15).

Using a defined protocol, we prospectively studied 35 patients with renal masses diagnosed during the last two years (Fig. 1). The experience with this group of patients is presented.

Materials and Methods

Patients with renal masses diagnosed by IVP and/or nephrotomography were evaluated. Nephrosonography was used to differentiate a cystic, solid or mixed renal mass. A commercially available B-scan unit (Picker 80L-D1) and a 3.5 MHz (13mm diameter) MIF transducer was utilized to maximize visualization of kidney and the internal structure of the lesion. Percutaneous renal cyst aspiration with a flexible system-thin wall 22 gauge Chiba needle with plastic connector to syringe under sonographic guidance was undertaken in patients whose sonogram demonstrated a cystic or mixed (cystic-solid) lesion. Renal masses found to be "solid" in the sonogram underwent sonographic evaluation of IVC and liver, searching for tumor spread. Prior to aspiration,

basic coagulation parameters were measured, as well as complete blood count, platelets and urinalysis. An informed consent was always taken.

Fluid obtained during renal cyst puncture was examined for:

- Color, turbidity, and translucency
- LDH, lipids, total protein, glucose
- Cytology
- Culture

Arteriography was performed in cases where a solid mass was found by sonography or when any parameter of cyst aspirate suggested malignancy or was doubtful. Complete angiographic evaluation, including mid-stream aortography, selective renal arterial injection and renal vein evaluation for tumor extension and liver metastases was performed.

Results

Since October 1978 we have performed thirty-five sonographically guided punctures of sonolucent or mixed renal masses. In the first ten cases,

TABLE I
Renal Mass Aspiration Results

Patient	History	Color Translucency	Cytology	HISTOCHEMISTRIES		
				LDH 100-225 MU/ML	CHOL. 120-280 GM %	T. P. 6-8-5 GM %
1	Asymptomatic L & R Renal Mass	Clear-Yellow	No Malig. Cells	19	22	15
2	Asymptomatic L Renal Mass	Dry Tap *	Inflammatory Cells	16	20	1.5
3	Asymptomatic L Renal Mass	Clear-Yellow	No Malig. Cells	22	20	2.5
4	Asymptomatic R Renal Mass	Clear-Yellow	No Malig. Cells	31	11	2.1
5	Asymptomatic R Renal Mass	Clear-Yellow	No Malig. Cells	24	10	0.8
6	Nephrolithiasis	Clear-Yellow	No Malig. Cells	12	26	2.1
7	Asymptomatic R Renal Mass	Clear-Yellow	No Malig. Cells	13	14	2.1
8	Asymptomatic L Renal Mass	Clear-Yellow	No Malig. Cells	28	29	0.9
9	Ureterolithiasis	Clear-Yellow	No Malig. Cells	45	3	1.3
10	Recurrent Calculii	Clear-Colorless	No Malig. Cells	23	12	2.0
11	Asymptomatic L Renal Mass	Clear-Yellow	No Malig. Cells	5	5	0.3
12	Renal Stone	Clear-Yellow	No Malig. Cells	24	9	1.9
13	Recurrent Uti	Clear-Yellow	No Malig. Cells	2.0	5	0.85
14	Back Pain	Clear-Yellow	No Malig. Cells	5.0	5	0.3
15	Microhematuria	Clear-Yellow	No Malig. Cells	25	0	2.0
16	Asymptomatic L Renal Mass	Clear-Yellow	No Malig. Cells	9	11	2.0
17	Nephrolithiasis	Clear-Yellow	No Malig. Cells	2	36	1.8
18	Hematuria	Clear-Amber	No Malig. Cells	6.9	84	4.1
19	Hematuria	Amber-Clear	No Malig. Cells	6.9	84	4.1
20	Asymptomatic R Renal Mass	Clear-Yellow	No Malig. Cells	28	23	1.8
21	Asymptomatic L Renal Mass	Clear-Yellow	No Malig. Cells	9	9	2.5
22	Microhematuria	Clear-Yellow	No Malig. Cells	25	39	2.6
23	Asymptomatic R Renal Mass	Clear-Yellow	No Malig. Cells	9	1	2.1
24	Microhematuria	Clear-Yellow	No Malig. Cells	0.3	21	2.8
25	R Flank Pain	Clear-Yellow	No Malig. Cells	25	36	2.1
26	Hematuria	Clear-Yellow	No Malig. Cells	35	40	4.0
27	Gross Hematuria Bilat	Clear				
	Renal Mass 1969 - Left	Coca-Cola	No Malig. Cells	31	24	3.0
28	Asymptomatic L Renal Mass	Clear-Yellow	No Malig. Cells	16	20	1.5
29	Asymptomatic L Renal Mass	Clear-Yellow	No Malig. Cells	7	6.3	
30	Asymptomatic Bilat Renal Mass	Clear-Yellow	No Malig. Cells	18	33	
31	Asymptomatic Bilat Renal Mass	Clear-Yellow	No Malig. Cells	24	32	3.07
32	Asymptomatic Renal Mass	Clear-Yellow	No Malig. Cells	31	26	
33	Asymptomatic Renal Mass	Clear-Yellow	No Malig. Cells	8	17	1.41
34	Asymptomatic Renal Mass	Clear-Yellow	No Malig. Cells	12	20	1.2
35	L Flank Pain 46	Dry Tap X 3				

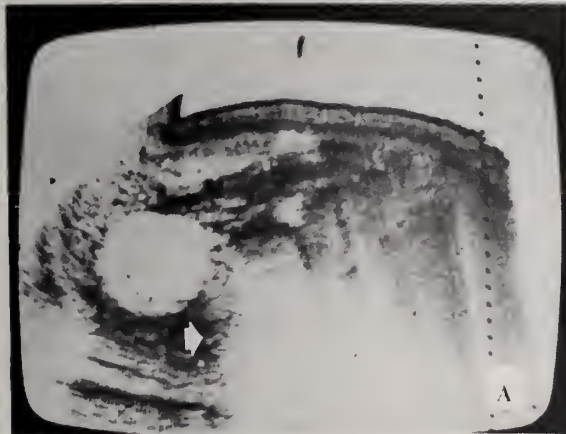
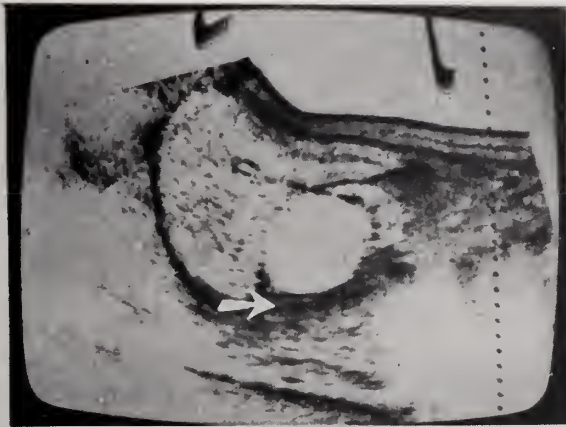


Figure 2: a) Renal cyst sonographically diagnosed by a sonolucent (echo-free) mass with distinct margination, refractive edge-shadowing (arrowhead) and distal acoustic enhancement (arrow). b) Cystogram: Water soluble (Conray-60) contrast injected to study margins of lesions.

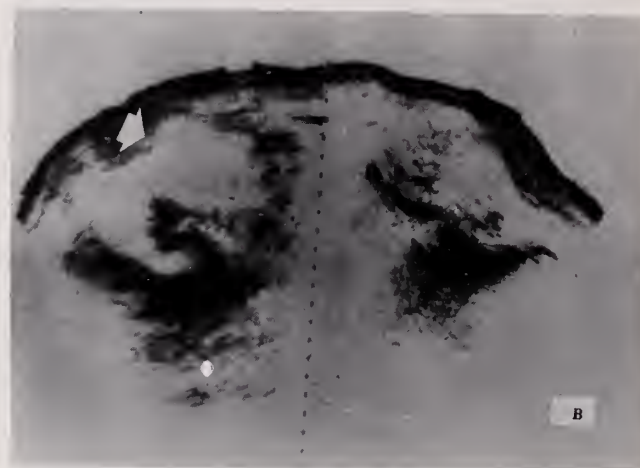
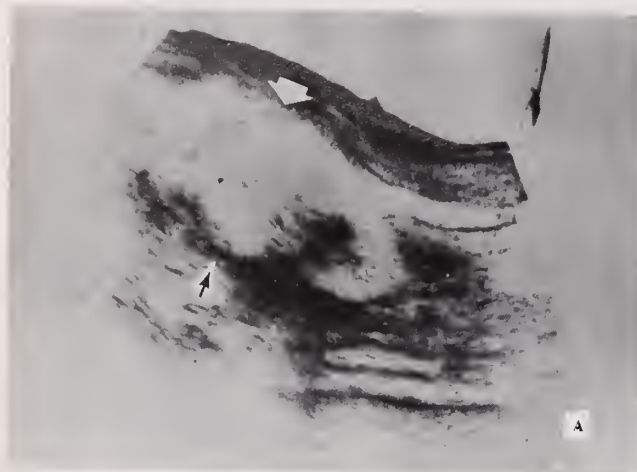


Figure 3: Mixed renal mass, relatively sonolucent but with few low level echoes within it (arrowhead). Distal acoustic enhancement (arrow) not so prominent. Diagnosis — transitional cell carcinoma.

surgery always followed as definitive procedure. Twenty eight patients were hospitalized 2 to 3 days to have the procedure. As experience increased, and as other reports suggest (14), the procedure was done on ambulatory basis. Follow-up sonograms are performed at 6 months and then yearly.

Table 1 summarizes our experience. Ninety-four percent (33 of 35) of our cases had proven benign renal cysts. In all but one case the aspirate was clear yellow. Case 27 had a clear Coca-cola like fluid aspirated from the right kidney and underwent arteriography and surgery which demonstrated a hemorrhagic benign renal cyst. Interestingly, he had had a left renal hemorrhagic cyst unroofed surgically 10 years prior to our evaluation. Figure 2 shows renal cyst sonographic characteristics.

In one of our cases the diagnosis of tumor was made (2.86 percent). The sonogram showed a fairly cystic mass with few low-level echoes within it. (Figure 3) Although the needle was placed in the center of the lesion, three times, a "dry-tap" resulted. Unfortunately, for technical reasons we were unable to obtain a saline flush of the area. A CT

scan suggested a cystic mass but posterior flank wall invasion indicated malignancy (Figure 4). The angiogram indicated few tumor vessels and encasement of arteries, compatible with malignancy (transitional cell carcinoma likely), or a large inflammatory mass (Figure 5). At surgery, transitional cell carcinoma with muscle invasion and liver metastasis was found. The patient died, three months later with pulmonary metastases.

The other "dry-tap" aspiration died of an unrelated cause. The autopsy revealed an old infarct in left kidney (Case 2).

Discussion

Benign renal cysts in our series had low LDH, usually below 25 μ u/ml. Cholesterol total proteins were also low. Glucose levels were variable and in some cases were higher than blood levels. None of the aspirates demonstrated malignant cells. Our results agree with other series (1, 5, 6, 7, 9, 13-15).

Tumor with or without associated cysts has



Figure 4: Contrast enhanced CT Scan on same patient as Figure 3 shows a relatively cystic mass but posterior flank wall invasion (arrows) indicate malignancy.



Figure 5: Arteriogram on same case as Figure 3 large left renal mass with encasement of arteries (arrowheads) and few tumor vessels (arrows).



been reported to yield a bloody or murky aspirate with high fat, high protein, low LDH, low or normal glucose (1, 5, 7, 9, 13-15). The presence or absence of malignant cells, cytologically examined, is not very reliable due to lack of exfoliation of adenocarcinoma cells (14). Adenocarcinoma is the most common malignant renal tumor.

Inflammatory masses have been reported to yield clear, murky or bloody fluid on aspiration. Mild elevation of fat and protein and very high LDH has been found (1, 5, 7, 9, 13-15). We had no inflammatory masses in our series.

Masses smaller than 2cm diameter are very hard to get to and we prefer to follow them with so-

nography every 6 months, if they appear completely cystic.

The reported incidence of complications with cyst puncture is 3.4 percent with very few needing surgery (11). Lang analyzed the complications of cyst puncture in 5674 cases of 84 institutions (11). Major complications such as hematoma, pneumothorax, arteriovenous fistula, infection, occurred in 10 percent (11). We had no major complications. Microhematuria occurred, in first post procedure urine, in 8.6 percent of our cases (3 of 35).

In analyzing factors influencing complication rate Lang found that experience is the most important one. Only 0.4 percent major complications occurred in centers with more experience, while 4.4 percent occurred in those with limited experience (11).

A single case of needle tract tumor seeding has been reported, and an 18 gauge needle was used (12).

In conclusion our study of 35 renal cyst punctures demonstrates that renal cyst aspiration is a safe, accurate procedure that should be routinely used for evaluation of asymptomatic renal cystic masses. The presented protocol for evaluation of these lesions should allow better use of medical resources with decreased morbidity and mortality to patients.

Acknowledgement

We wish to acknowledge the cooperation of Dr. Laura Lespier, Nephrologist, VA Hospital, who referred most of our patients.

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Adverse Reactions: Gastrointestinal System—The most frequent adverse reactions which occurred were gastrointestinal: nausea, 1 in 9 patients; dyspepsia, 1 in 10 patients; abdominal pain, 1 in 15; gastrointestinal distress, 1 in 15; flatulence, 1 in 25; diarrhea, 1 in 25; constipation, 1 in 40; vomiting, 1 in 30; gastritis, 1 in 55; and significant gastrointestinal bleeding without evidence of peptic ulceration, 1 in 240.

The incidence of peptic ulcer in about 3000 patients treated up to two years in clinical studies was about 1 in 50. Thirty-four percent of the ulcer patients had prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs, including corticosteroids, known to produce peptic ulceration.

In clinical trials about 10% of patients dropped out because of adverse reactions, mostly gastrointestinal in nature.

Body as a Whole—headache, about 1 in 10 patients; asthenia and chest pain, less frequently; and, rarely, anaphylactoid reactions.

Cardiovascular—edema, about 1 in 15 patients; hypertension, less frequently.

Central Nervous System/Psychiatric—dizziness or lightheadedness, about 1 in 20 patients; tension or nervousness, 1 in 50 patients; drowsiness, 1 in 60 patients; insomnia and depression, less frequently.

Dermatologic—rash, about 1 in 40 patients; pruritus, 1 in 60 patients; skin irritation, 1 in 55 patients.

Special Senses—tinnitus, about 1 in 65 patients.

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THE PREVALENCE OF THERMOPHILIC ACTINOMYCETES IN SUGAR CANE RELATED ENVIRONMENTS, AND PRECIPITINS IN THE POPULATION IN PUERTO RICO

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Viswanath P. Kurup, PhD
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Summary: The study shows the major thermophilic actinomycetes isolated from sugar cane related environments and other environmental samples in the Southern Coastal Plains of Puerto Rico are *Thermoactinomyces candidus* and *T. vulgaris*. Air samples show that large numbers of thermophilic actinomycetes are isolated when sugar canes are burned while none are isolated when airborne particles from burnt sugar cane were not present.

The most prevalent thermophilic actinomycetes antigen in Puerto Rico is *T. sacchari* (18.2 percent) on the basis of the presence of precipitating antibodies, followed by *T. candidus* (10.7 percent) and *T. vulgaris* (8.2 percent).

Resumen: Estudios de nuestras relacionadas a la caña de azúcar y otras fuentes ambientales demuestran que los dos principales actinomicetos termofílicos aislados en las planicies de la costa Sur de Puerto Rico son *Thermoactinomyces candidus* y *T. vulgaris*. Muestras de aire tomadas al momento que hay quema de la caña demuestran la aislación de un gran número de actinomicetos termofílicos mientras que los resultados son negativos cuando no hay quema de la caña.

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En base a la prueba serológica de anticuerpos precipitantes, el antígeno de actinomicetos termofílicos más prevalente en Puerto Rico es *T. sacchari* (18.2 por ciento) seguido de *T. candidus* (10.7 por ciento) y *T. vulgaris* (8.2 por ciento).

Introduction

Thermophilic actinomycetes are implicated in several types of hypersensitivity pneumonitis. These include, bagassosis (1, 2) farmer's lung (3, 4, 5) mushroom worker's lung (6), air conditioner (7, 8), and humidifier induced (9, 10), hypersensitivity pneumonitis. Organisms frequently associated with those conditions include *Micropolyspora faeni*, *Thermoactinomyces vulgaris*, *T. candidus*, *T. sacchari* and *Saccharomonospora viridis*. These organisms grow in materials or substrates with elevated temperatures such as moldy hay, bagasse, compost, etc. Of particular interest is bagasse, the fibrous crushed product of sugar cane which promotes the growth of *T. sacchari* and the antigen associated with bagassosis. As sugar cane is cultivated as a major agricultural crop in this part of the country the prevalence of *T. sacchari* in bagasse and their role in hypersensitivity pneumonitis needed study.

The present study was undertaken with a view to investigate the prevalence of thermophilic actinomycetes in bagasse, soil sugar cane fields, airborne particulate matter from burned sugar cane crops, and other natural environments such as soil, vegetable matter, compost, and animal dung. In addition to the isolation and identification we also studied circulating antibody against thermophilic actinomy-

TABLE I
Methods of Procedure in Culturing

	Processing and Inoculum	Culture Media	Expected Microorganisms	Temperature
I.	Whole sample, culture directly	Trypticase Soy Agar No. 1 No Antibiotics Trypticase Soy Agar No. 2 30 ug/ml Novobiocin Half Strength Nutrient Agar No. 3 No Antibiotics Half Strength Nutrient Agar No. 4 30 ug/ml Novobiocin	Thermophilic Actinomycetes	55°C
II.	1.25 G., 2.5 G., and 10.0 G. in 50 ml. 0.85 percent sterile saline, 0.5 ml. inoculum	TSA No. 1, TSA No. 2 N. A. No. 3, N. A. No. 4	Thermophilic Actinomycetes	55°C
III.	Exposed plates air samples, 15 minutes	TSA No. 1, TSA No. 2	Thermophilic Actinomycetes	55°C

cetes in the sera of persons living in this area considered to be exposed to these organisms. The results of the study is presented and the significance of the results discussed.

Materials and Methods

Collection of samples and methods of procedure in culturing:

A total of 210 samples from sugar cane related environments and other ambient environments were collected from various parts of the island from November 10, 1978 to March 21, 1980 and studied for the presence of thermophilic actinomycetes.

The samples were collected in sterile whirl-pak bags and processed as soon as they were brought to the labora-

tory. A portion of each specimens were cultured directly on Trypticase Soy and Nutrient Agars (Table I). The inoculated plates were incubated as mentioned above. Plates were examined at the end of 2, 3, 5, and 10 days, and suspected colonies were removed, purified, and presumptively identified by morphology and biochemical tests. These tests include decomposition of casein, tyrosine, xanthine, hypoxanthine, esculin, and starch (23).

Air samples of airborne burned sugar cane particles from burned sugar cane fields for thermophilic actinomycetes were done by exposing Trypticase Soy Agar plates (Table I) for 15 minutes. The plates were incubated and colonies were identified as described above:

Sera for precipitins:

A total of 159 serum samples were studied for the presence of precipitin antibodies against thermophilic actinomycete antigens. Of the 159 sera, 128 samples were co-

TABLE II

Thermophilic Actinomycetes Isolated from Sugar Cane
Products and Related Environments

Samples	No.Studied	No.Positive	O r g a n i s m s I s o l a t e d				
			T.candidus *	T.vulgaris	Thermo- Actino- myces Species	M.faeni +	Other =
Bagasse	23	12	9	8	1	0	0
Sugar Cane Compost	2	2	2	2	0	0	0
Sugar Cane Stem and Leaves	3	2	2	1	0	0	0
Soil Sugar Cane Field	19	14	7	9	1	1	0
Air Samples— Burned Airborne Sugar Cane Particles							
Evidence of Fallout	49	19	6	6	8	0	3
No Evidence of Fallout	51	0	0	0	0	0	0
Total -	147	49	26	26	10	1	3

* Thermoactinomyces

+ Micropolyspora

= Other thermophilic Actinomycetes

llected from March 1976 to November 1977 in three geographical areas, North, Central-East, and South of Puerto Rico as described in previous work (15). Thirty one samples were collected from October 1978 to July 1979 in the Southern part of Puerto Rico from patients at the Workmens Compensation State Fund and Damas Hospital suspected of a hypersensitivity pneumonitis or an unknown bronchopulmonary problem.

Agar gel diffusion test:

Lyophilized antigens of *Micropolyspora faeni* 5.0 mg/ml, *Thermoactinomyces vulgaris*, *T. candidus*, and *T. sacchari* at 30 mg/ml were used for gel immunodiffusion. Antigen from *M. faeni* was prepared by growing in a synthetic medium according to the method of Kurup and Fink (16), while the antigen from other thermophilic actinomycetes was prepared by a modified method (17) of the double dialysis

antigen preparation of Edwards (18). For the gel immunodiffusion test a modification of the Wadsworth template double immunodiffusion method (19) was used to test the sera for the presence of precipitating antibodies against thermophilic actinomycetes (20). Antigen preparation and gel immunodiffusion test was performed as previously described (15).

Results

Table II illustrates the various specimen samples of sugar cane products and related environments studied and the thermophilic actinomycetes isolated. Of the 147 samples studied, 49 yielded thermophilic actinomycetes. A total of 66 strains belonging to *Thermoactinomyces candidus*, *T. vulgaris*, *T. in-*

TABLE III

Thermophilic Actinomycetes Isolated from Environmental Samples

	No.Studied	No.Positive	Organisms Isolated				
			T.candidus +	T.vulgaris	T.intermedius	Thermo-Actino-Myces Species	Other =
Soil	4	3	2	3	0	1	0
Leaf Compost	26	20	7	14	1	11	2
Coffee Bean Peelings	1	1	1	1	0	0	0
Hay	3	3	3	0	0	1	0
Sawdust	8	7	6	0	0	1	0
Horse Dung	4	3	3	1	0	0	0
Cow Dung	15	15	8	12	0	6	0
Sheep Dung	2	2	2	0	0	1	0
Total -	63	54	32	31	1	21	2

+ Thermoactinomyces

= Other Thermophilic Actinomycetes

intermedius, *Thermoactinomyces* sp., *Micropolyspora faeni*, and other thermophilic actinomycetes were isolated.

The results of the study indicate that the most prevalent thermophilic actinomycete isolated from bagasse and other sugar cane related environments as well as in the general environmental samples (Table III) is *T. candidus*, closely followed by *Y. vulgaris*, *T. sacchari* was not isolated from any of the samples studied.

The results of the serological study (Table IV) demonstrated that the most prevalent precipitin reaction in Puerto Rican sera against thermophilic actinomycetes occurs with *T. sacchari* (29 of 159 or 18.2 percent). Other reactions included 17 *T. candidus* (10.7 percent), 13 *T. vulgaris* (8.2 percent), 5 *M. faeni* (3.1 percent), with 103 sera not reacting

(64.8 percent) to any of the antigens studied. Of the 159 sera tested with thermophilic antigens, 47 (29.5 percent) reacted only to one antigen, 3 (1.9 percent) to two antigens, and 6 (3.8 percent) to three or more antigens.

Discussion

It is interesting to note that in our study *Thermoactinomyces candidus* was isolated from all types of samples studied including bagasse, sugar cane related products, air samples such as soil, leaf compost, hay, sawdust and different animal dungs. The study also indicates that *T. sacchari* has a wider distribution than any of the other thermophilic actinomycetes. Similar results have been obtained by other workers (20) when isolating thermophilic actinomy-

TABLE IV
Results of the Immunodiffusion Tests

Antigens	Number of Positive Reactions				Percent Positive	No. of Samples Tested
	S	W	EW	POS		
M. faeni T-150	0	0	5	5	3.1	159
T. vulgaris T-101	0	1	12	13	8.2	159
T. candidus T-106	0	2	15	17	10.7	159
T. sacchari T-145	0	2	27	29	18.2	159

EW = questionable

W = single less dense discernible precipitin band

S = multiple dense intensely stained precipitin band

cetes from the environment such as, air conditioners, humidifiers, wood and house dust, moldy grains and others. In the present study it was found that the most prevalent thermophilic actinomycete is *T. candidus*, closely followed by *T. vulgaris*.

In contrast to the work of Lacy (13) who had a high percentage of *T. sacchari* isolation from bagasse, we have not isolated this organism, in our study. It is possible that our method is not appropriate for isolation of *T. sacchari*. It is known that actinomyceetes, such as *Streptomyces* from soil will grow well in low nutrient and slightly alkaline media (21). Use of half strength nutrient agar was established toward the end of the study with the idea of the competition that may have been caused by the high number of isolation of *T. candidus*, *T. vulgaris* and other thermophilic actinomycetes but at this moment we cannot evaluate this approach because of insufficient number of samples.

It is of importance to note the high prevalence of thermophilic actinomycetes during the burning season of sugar cane (Figure 1). While none of them were isolated in the absence of airborne particles from burnt sugar canes. *Thermoactinomyce-*

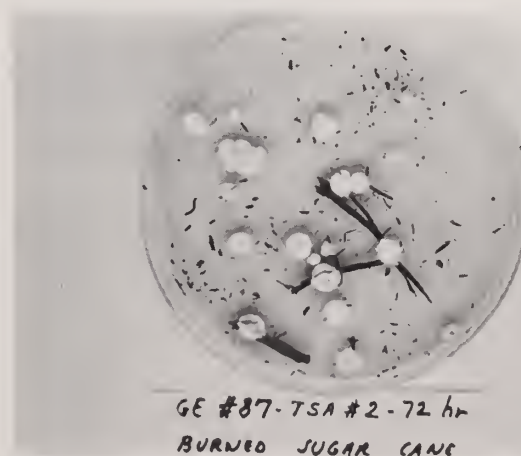


Figure 1: Trypticase Soy Agar plated exposed in the air 15 minutes during sugar cane burning season. The burned particles may be seen as black debris over the plate. In 72 hours several colonies of the thermophilic actinomycetes grew also in the plate.

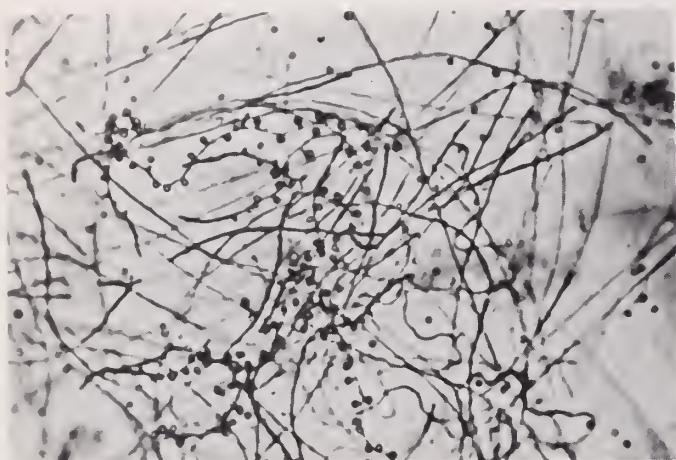


Figure 2: Smear of *T. vulgaris* culture showing spores produced either directly on the hyphae or on small stalk X 1100.

tes vulgaris which was isolated in the air samples (Figure 2) during the fallout of airborne sugar cane particles is known to be an etiological agent in bagassosis. *T. candidus* was isolated in the air samples in the same proportion as *T. vulgaris*. The high prevalence of thermophilic actinomycetes as well as the high quantities of burned organic particulate matter reaching the lung may be responsible for damage to the lung but needs further study.

It is interesting to note the isolation of *Thermoactinomyces intermedius* a recently described species of thermophilic actinomycete, from leaf compost (23). The finding of a high percentage of isolation of thermophilic actinomycetes from the general environment suggests that the necessary conditions are present in Puerto Rico for the maintenance of these organisms in nature. The evidence that large numbers of thermophilic actinomycetes were present in the air samples when the sugar canes were burned, is indicative of a major health hazard and needs further study.

The prevalence of a high number of thermophilic actinomycetes and the presence of precipitating antibodies in the sera of persons living in the sugar cane environment of Puerto Rico leads us to suspect that some of them may have experienced hy-

persensitivity pneumonitis, however, this needs further clarification. It is also possible that the so called "transient 24-48 hours flu" and "transient 24-48 cold" seen in clinics and which show no supportive clinical and laboratory evidence may be cases of hypersensitivity pneumonitis. The results also suggest that some of the precipitin positive individuals may eventually develop hypersensitivity pneumonitis by continuous exposure to these thermophilic actinomycetes in the airborne particle.

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REITER'S SYNDROME
SKELETAL AND CARDIAC SCANS

Lorraine Vázquez de Corral, MD
Edwin Mejías, MD
Julio V. Rivera, MD

Case Summary

A 46 year old male with history of arterial hypertension, pyuria, and recurrent iridocyclitis developed swelling of the right knee approximately four weeks prior to admission. Swelling extended progressively to include the whole right leg and was accompanied by mild tenderness and rubor. On admission he also complained of swelling and pain of his left second toe.

There is history of occasional joint stiffness. Patient denies fever, diarrhea, low back pain, or venereal disease.

Physical examination revealed a well developed well nourished male. Temperature: 38.6°C; pulse: 62/min; blood pressure: 160/60mm Hg. Eye examination was normal. Heart examination revealed a grade I/II systolic ejection murmur and a grade II/VI diastolic murmur heard best along the left sternal border. There was swelling of the right leg with increased temperature and tenderness on palpitation. Mild swelling and pain at the second metatarsophalangeal joint of the left foot was also present. A few keratotic plantar lesions were noted.

Pertinent laboratory data included a markedly elevated sedimentation rate, negative rheumatoid factor and antinuclear antibody. Histocompatibility antigen HLA-B27 was present. Joint fluid analysis revealed an inflammatory fluid with increased cellularity and increased complement levels. Serum C₃ levels were also elevated. Urinalysis showed pyuria without bacteriuria. Urine cultures were nega-

tive.

Electrocardiogram revealed a first degree A-V block. Echocardiogram showed a dilated aortic root with thickening of the aortic valve.



Figure 1: Roentgenogram of the pelvis reveals marked sclerosis of the margins of both sacroiliac joints.

From the Medical and Nuclear Medicine Services, Veterans Administration Medical and Regional Office Center and the University of Puerto Rico School of Medicine, San Juan, Puerto Rico.



Figure 2: Scintiphotos (^{99m}Tc Medronate) of the spine demonstrate multiple asymmetric segmental sites of increased localization.



Figure 3: Scintigram (^{99m}Tc Medronate) of the pelvis shows symmetrically increased localization in the sacroiliac joints.

Radiograph (Fig. 1) of the lumbosacral spine revealed minimal lumbar spondylosis changes. The intervertebral spaces were well maintained. There was marked sclerosis with some erosion of the margins of both sacroiliac joints compatible with a moderately advanced sacroileitis.

Bone scan (^{99m}Tc Medronate) (Fig. 2, 3) revealed scoliosis of the spine and uneven distribution of activity in the dorsal region most marked in several costovertebral articulations. The activity noted in the sacro-iliac joints was symmetrically increased. There was also increased localization of activity in the right knee, right ankle, and the second metatarsophalangeal joint of the left foot. This study is compatible with inflammatory polyarthritis.

A multigated cardiac blood pool study (^{99m}Tc -RBC's) (Fig. 4) revealed severe aortic insufficiency with good ventricular function. Left ventricular ejection fraction was 66 percent. Wall motion was adequate. Left/right ventricular stroke volume ratio was 3.6.

Comments

Reiter's syndrome consists of the triad urethritis, conjunctivitis or uveitis, and arthritis. Hyperkeratotic skin lesions, buccal ulcerations and balanitis may also form part of the clinical picture (1, 2). The histocompatibility antigen HLA-B27 is associated to this entity (1-4). This disease predominates in males between the ages of 20 to 30 years. Its precipitating event is unknown and there is no cure (1). Recent studies show that most patients have persisting symptoms that may lead to chronic disability in contrast to earlier views which considered Reiter's a self-limiting disease (2, 3). Late manifestations of Reiter's syndrome, although rare, are becoming increasingly recognized, the most frequent

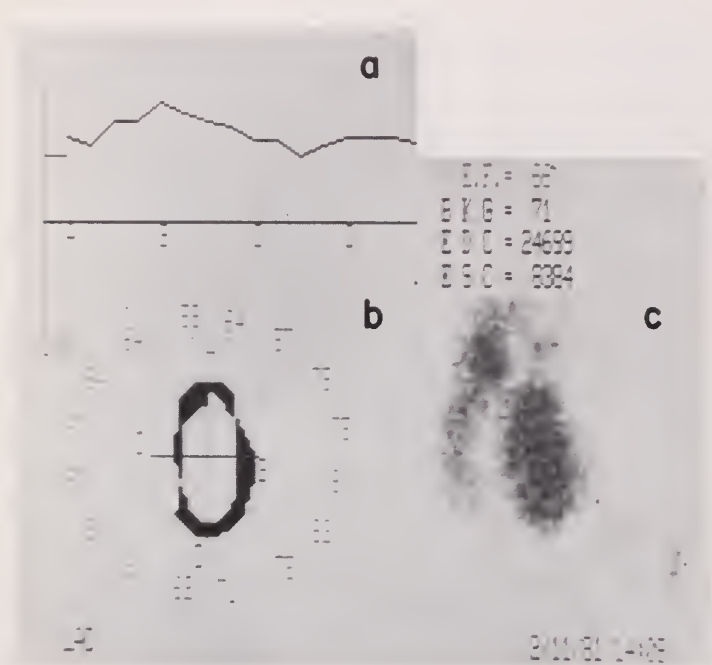


Figure 4: Analysis of left ventricular function, multiple gated blood pool study (^{99m}Tc -RBC).

a. Graph of segmental wall motion corresponding to regions presented in b.

b. Circumferential analysis of wall motion (regional ejection fraction). Numbers and width of gray zone represent degree of segmental motion.

c. End diastolic image. Note hypertrophy of left ventricular wall (clear zone).

being aortic regurgitation and conduction defects (1, 4).

Radiologic changes are often absent or minimal in early Reiter's disease (1). Bone imaging with ^{99m}Tc -labelled phosphate compounds is very effective in detecting early lesions (5-8). In the present case increased asymmetrical activity in the dorso-lumbar spine was observed by bone scintigraphy in contrast to only minimal lumbar spondylotic changes in radiography.

The mechanism of increased concentration of ^{99m}Tc phosphate compounds around inflamed joints is considered secondary to the increased bone blood flow contributed by branches of synovial vessels. The increased blood flow and increased surface area from capillary recruitment enables the radionuclide to diffuse to the bone in larger amounts

(7-8).

The sacroileitis observed may be quantified by computer analysis. An increased sacroiliac to sacral ratio of activity in patients suspected clinically to have Reiter's or ankylosing spondylitis has been found especially in those who are HLA-B27 + (5). Although quantitative scintigraphy is a valuable technique for establishing the presence of sacroiliac disease, an increased sacroiliac to sacral ratio is clearly not specific nor diagnostic of this disease. However, recent studies have concluded that the radionuclide approach is more sensitive than conventional radiography in this condition (5-7).

Some patients with Reiter's syndrome have aortic regurgitation and when they do spondylitis is nearly always present. The cardiovascular lesion has been described anatomically as a dilatation of the aortic root. This large vessel arteritis is often asymptomatic until it presents as a post-inflammatory aortic regurgitation (9, 10). Extension of fibrous tissue to the muscular ventricular septum is also characteristic and explains the associated conduction disturbances. Although the frequency of aortic regurgitation in patients with Reiter's syndrome or ankylosing spondylitis is unclear, it does appear to increase with increasing duration of arthritis and worsens the prognosis (10).

Radionuclide imaging and cineangiography may be useful in detecting the presence and evaluating the severity of the aortic regurgitation present in Reiter's. The radionuclide used for cardiac blood pool imaging is ^{99m}Tc bound to red blood cells. This is mediated by an injection of stannous ion which appears to change red blood cell membrane to permit the binding of subsequently injected ^{99m}Tc (12). Absence of immediate risk and relatively low radiation dose are desirable features of this procedure.

The gated blood pool study (synchronization of scintillation camera images with the electrocardiogram) using ^{99m}Tc labelled erythrocytes is found to be most useful in the assessment of global ventricular function, regional wall motion and valve regurgitation (11, 13). Valve regurgitation can be assessed by comparing right and left ventricular stroke volumes. Normally the stroke volume of the right ventricle is equal to that of the left ventricle. In aortic regurgitation left ventricular stroke volume

will be greater in order to maintain an adequate cardiac output (13-14). In our patient marked aortic regurgitation was assessed in view of a left/right ventricular stroke volume ratio of 3.6.

For some Reiter's syndrome may be a self limiting disease but for others it may be an important chronic systemic disease of uncertain prognosis. Radionuclide bone imaging and left ventricular function studies have been shown to be useful in assessing the extent and activity of this condition and may help as prognostic criteria in the follow-up evaluation of individual patients.

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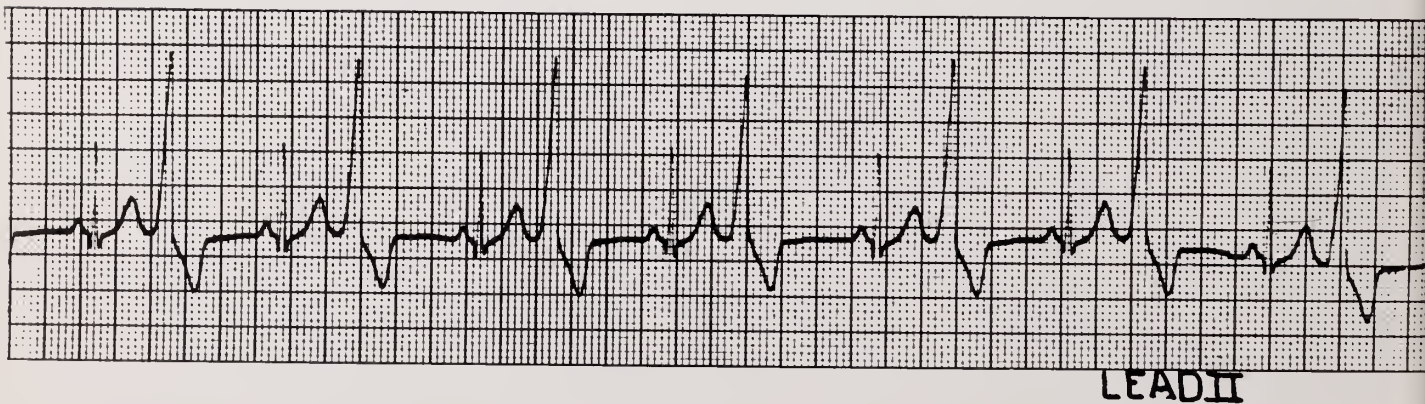
CASOS DE ELECTROCARDIOGRAFIA PEDIATRICA



Rafael Villavicencio, MD

W. G. es un niño de 3 años de edad referido para evaluación de una arritmia detectada durante un examen por una infección persistente de las vías respiratorias altas. No hay evidencia de síncope, palpitaciones, dolor precordial, ni enfermedad cardíaca en su historial pasado.

En el momento de su examen se hallaba asintomático, y se obtuvo el siguiente trazado electrocardiográfico:



El diagnóstico más probable es:

- a) Bloqueo de rama intermitente
- b) Bigeminismo ventricular
- c) Prematuros ventriculares multifocales
- d) Contracciones ectópicas supraventriculares

RESPUESTA

b) Bigeminismo Ventricular

El bigeminismo ventricular lo componen contracciones prematuras ventriculares (CPV) alternando con latidos sinusales. Las presentes en el trazado son unifocales, pues todas tienen la misma morfología.

En términos generales, las CPV tienen las siguientes características que nos ayudan a reconocerlas:

- 1) ausencia de ondas P
- 2) complejos QRS abigarrados, de morfología diferente, y mayor duración que el QRS normal
- 3) onda T prominente y en dirección opuesta a la del complejo QRS normal
- 4) pausa compensatoria luego de la CPV

El bigeminismo ventricular puede estar presente en niños con corazones normales bajo la influencia de factores precipitantes como: desbalance electrolítico, "stress", cateterismo cardíaco, hipoxia, y medicamentos (isoproterenol, digoxin, imipramina). También pueden estar presentes en miocardiopatías, cardiopatías congénitas (anomalía de Ebstein, defectos septales) y luego de cirugía cardíaca.

Tratamiento

El bigeminismo ventricular en niños se considera benigno y no requiere tratamiento cuando:

- 1) no hay cardiopatía asociada
- 2) es unifocal
- 3) desaparece con el ejercicio
- 4) el intervalo QT en reposo es normal
- 5) no produce síntomas (dolor precordial, palpitaciones, o síncope)

Si no es benigno por los criterios arriba mencionados, entonces debe recibir tratamiento médico (1):

A) Agudo:

- 1) Propranolol ---- si el miocardio no está afectado es el medicamento indicado en el bigeminismo ventricular. Dosis: 0.01 a 0.05 mg/Kg IV en 5 minutos.
- 2) Lidocaína ---- es el medicamento de elección en la fase aguda si ocasiona taquicardia ventricular. Se administra en bolos endovenosos de 0.5 a 1 mg/Kg.
- 3) Difenhidantoína ---- cuando es causado por niveles tóxicos de digoxin. Dosis: 3-5 mg/Kg IV en 5 minutos.

B) A largo plazo:

- 1) Propranolol ---- 1-4 mg/Kg/ día en 4 dosis.
- 2) Sulfato de quinidina ---- 10-20 mg/Kg/día en 4 dosis.

Pronóstico

Aunque se considera de buen pronóstico, el bigeminismo ventricular tiene el potencial de iniciar una taquicardia ventricular (2), en cuyo caso el pronóstico ya deja de ser bueno.

Reconocimiento

El autor quiere reconocer la valiosa cooperación que en la preparación de esta nueva Sección recibió del Dr. Jaime Deseda, Director del Departamento de Pediatría de la Escuela de Medicina de la Universidad del Caribe en Cayey.

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1. Goldfarb M. Comparative duration of antibiotic treatment for urinary tract infections. Presented as a Scientific Exhibit at the American Academy of Family Physicians Annual Convention and Scientific Assembly, San Francisco, Calif. Sept 25-28, 1978.

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TWO DIMENSIONAL ECHOCARDIOGRAPHY: EVALUATION OF A HEART MURMUR

I. Rivera, J. Couto and O. Jiménez
Cardiology Section Veterans Administration Hospital
San Juan, Puerto Rico

This 18-year-old male with a Grade II/VI midsystolic murmur was referred for evaluation. The murmur was best heard in the base and pulmonic area. The second heart sound was normally splitted and there was no click. The electrocardiogram was normal.

The two dimensional echocardiograms are shown below:

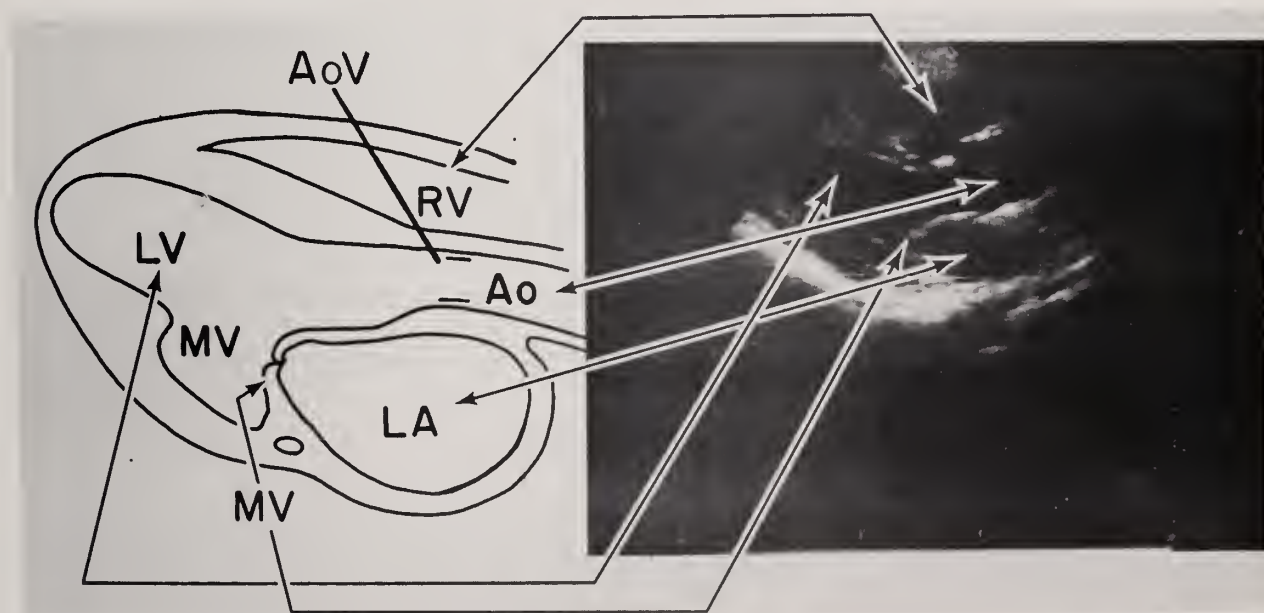


Figure 1: Longitudinal parasternal axial view at end of systole: RV: right ventricle, LV: left ventricle, Ao: aorta, LA: left atrium, M.V.: mitral valve, IVS: inter-ventricular septum, VSD: ventricular septal defect, AoR: aortic root.

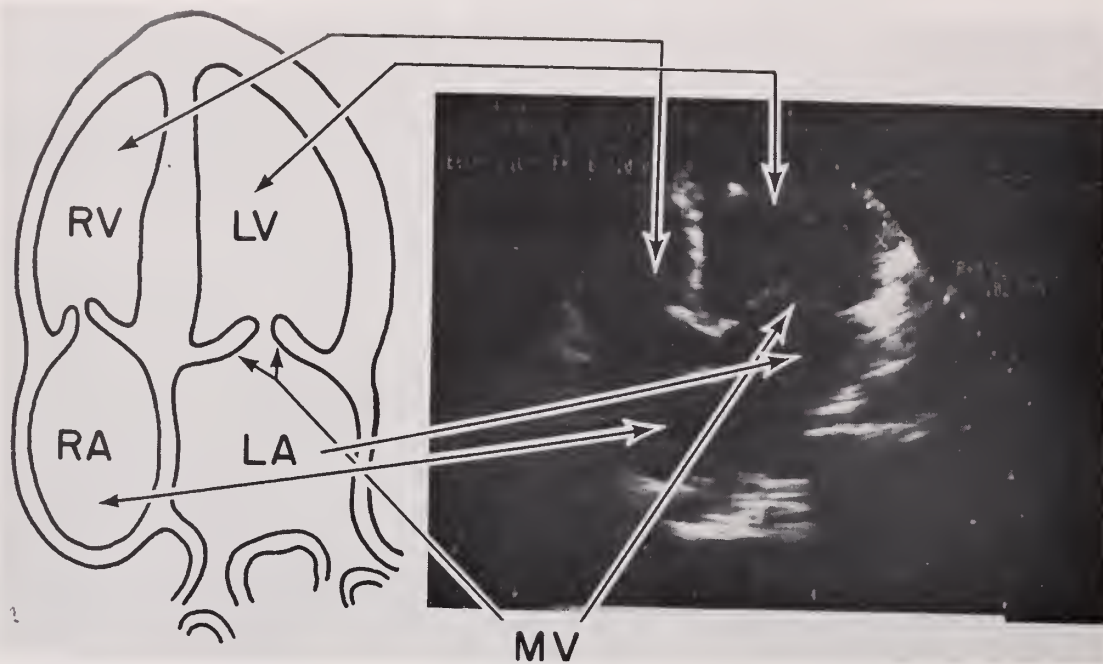


Figure 2: Four chamber apical view - RV: right ventricle, LV: left ventricle, Ao: aorta, LA: left atrium, MV: mitral valve, IVS: interventricular septum, VSD; ventricular septal defect, AoR: aortic root.

The most likely diagnosis is:

1. Aortic stenosis
2. Ventricular septal defect
3. Mitral valve prolapse
4. Functional murmur

The answer is number 4

The diagnosis of aortic stenosis is not sustained because there is no evidence of calcification or thickening in the aortic valve, which is fused with the echoes of the aortic walls. Also, there are no secondary changes in the left ventricle such as left ventricular hypertrophy or left atrial enlargement.

The continuity between the aorta and the interventricular septum (IVS), is intact. Most VSD are identified echocardiographically by a discontinuous interface between the aorta and the IVS; therefore a VSD is not the diagnosis. Defects in the IVS less than 3 mm can not be identified with this technique.

Note the appearance of the mitral valve in Figure 2. During systole, the anterior and posterior leaflets do not prolapse into the left atrium.

Considering the age of the patient and the normal echocardiographic evaluation, a functional murmur is the most likely diagnosis.

ABSTRACTOS DE LITERATURA MEDICA

EFFECTO DE LA THEOFILINA ORAL EN LA RESPUESTA A ISOPROTERENOL EN PACIENTES CON ENFERMEDAD OBSTRUCTIVA PULMONAR CRONICA

William Dull - University of Iowa - American Review Respiratory Diseases Vol. 123 No. 3 - marzo 1981, pág. 340-341.

El estudio está basado en dos premisas:

1. Que pacientes hombres con diagnóstico COLD pueden evidenciar un mejoramiento objetivo cuando son tratados con Teofilina oral. Dicha mejoría se evidencia al medir la capacidad vital forzada (FVC, FEV 1 y MVV). En este sentido su enfermedad tiene un componente reversible aunque sea crónica.

2. Es común antes de comenzar la terapia con teofilina el medir la respuesta de estos pacientes a la inhalación con Isoproterenol (Isuprel). Sin embargo esta prueba se hace en la mayoría de los casos mientras el paciente está recibiendo broncodilatadores orales.

El propósito del estudio era determinar si las preparaciones broncodilatadoras del tipo de las Metilxantinas debía ser interrumpidos antes de la prueba de Isuprel, pues los autores sospechaban que los resultados iban a ser distintos si los pacientes estaban tomando un placebo o una teofilina. Los autores usaron 38 hombres fumadores crónicos de cigarrillos que tuviesen obstrucción entre moderada a severa sin historial de asma bronquial previa y todos con el diagnóstico clínico de Bronquitis Crónica y/o Emfisema Pulmonar.

Dichos pacientes que luego de ser sometidos a tratamiento con metilxantinas fueron divididos al azar y de una manera doblemente ciega (doubleblind).

Los resultados demostraron que los pacientes a los cuales se les hace la prueba de Isuprel mientras están ingiriendo metilxantinas la respuesta broncodilatadora es menor que si estaban ingiriendo placebo al momento de la prueba. Los autores recomiendan el discontinuar la administración de teofilina antes de ejecutar la prueba de Isuprel.

El estudio no puede determinar por cuanto tiempo antes se debe discontinuar la administración de teofilina pero sugiere que la suspensión de la dosis previa a la prueba no sea suficiente y que sea necesario el suspenderla por un tiempo más prolongado.

(Sometido por Ramón E. Figueroa Lebrón, MD)

RENAL AND HEMODYNAMIC EFFECTS OF THE PERITONEOVENOUS SHUNT II LONG-TERM EFFECTS

Greig, P. D., Blendis, L. M., Langer, B. et al - Gastroenterology 80: 119, 1981.

Los autores habían reportado los cambios en la función renal y cardiovascular que ocurren tempranamente después de la construcción de un puente que lleva líquido de la cavidad peritoneal al sistema venoso (LeVeen o peritoneovenous shunt). En este artículo reportan estudios de balance de sodio, función renal (depuración de creatinina), niveles séricos de renina y aldosterona, función cardiovascular hechos en siete pacientes antes y de tres a treinta meses después de establecido el puente. Entre los hallazgos notables se encontró una mejoría significativa en la excreción urinaria de sodio y la función

glomerular renal. La presión portal bajó en promedio un 37 por ciento después de la cirugía.

Esta operación, que se recomienda en pacientes selectos con ascitis intractable a tratamiento médico, resulta en cambios fisiológicos beneficiosos que pueden perdurar un largo plazo permitiendo un manejo más efectivo de estos pacientes.

(Sometido por Angel Olazábal, MD)

ENVENENAMIENTO EN EPILECTICOS

Keith Nawton, Joan Fagg and Pamela Marsack from the University Department of Psychiatry, Warnerford Hospital, Oxford, Warnerford Journal of Neurology, Neurosurgery and Psychiatry, 1980, 43, 168-170.

En un estudio de pacientes admitidos durante 2 años al hospital después de envenenarse ellos mismos o de lesiones ocasionadas por ellos mismos, se encontró muchos pacientes con epilepsia comparado con la población general. Los hombres con epilepsia sobresalían en este grupo. Los pacientes con epilepsia habían hecho repetidos atentados. Anti-convulsantes particularmente barbitúricos fueron usados en la mayoría de estos envenenamientos.

(Sometido por Ramón E. Ortiz, MD)

ESTIMULACION NERVIOSA ELECTRICA TRANSCUTANEA Y ORTHOSIS EXTENSORA EN CONTRACTURA DE RODILLA EN ESCLERODEMA

Tewfik, E., Risk, M. D., Seung, Ja Pawk, M. D. - Arch. Phys. Med. Rehabil. 62: 86-88, 1981.

Una niña de 8 años de edad con una contractura en flexión de la rodilla secundario a enfermedad

esclerodérmica con hemiatrofia fue tratada con pad calientes, estiramiento gentil y una serie de orthosis posteriores. El arco de movimiento de la rodilla mejoró a 35° en un período de 16 semanas. Nueve meses después la contractura había mejorado. Como un método de tratamiento alternativo, se aplicó estiramiento continuo usando una ortosis de extensión al frente junto con estimulación nerviosa eléctrica transcutánea. La rodilla ganó un arco de movimiento de 55° en un período de 6 semanas.

(Sometido por E. Baucage, MD)

SENSORY CONDUCTION OF BRANCHES OF SUPERFICIAL PERONEAL NERVE

Izzo, K. L., Sridhara, C. R., Lemont, H., Rosenhottz, H. - Arch. Phys. Med. Rehabil. 62: 29-27, 1981.

Se evaluó un método para medir la velocidad de conducción sensorial de las ramas superficiales del nervio peróneo: Un pre-requisito esencial para el estudio de este nervio es el conocimiento exacto de su topografía. El método incluye el colorar los electrodos directamente sobre las ramas del nervio y estimular el nervio peróneo superficial en el aspecto anterolateral de la pierna. El valor promedio obtenido 2.8 m s e c. Esta técnica debe ser útil en la evaluación electrodiagnóstica de la neuropatía periférica y condiciones neuropáticas y de compresión del nervio peróneo o sus ramas sensoriales.

(Sometido por Jesús Maldonado, MD)

BRACHIAL PLEXUS LESIONS IN PATIENT WITH CANCER

Shashiddar H. Kori, MD, Kathleen M. Foley, MD and Jerome B. Posner, MD - Neurology, 31: 45-50, 1981.

En pacientes con cáncer, signos del plexo

braquial son usualmente causados por infiltración de tumores o lesiones de la terapia por radiación (RT). Nosotros analizamos 100 casos de plexopatía braquial para determinar qué criterios clínicos pueden ayudar para diferenciar tumores por lesiones de radiación. 78 pacientes tenían tumores [C3-4 con previa RT] y 22 tenían lesiones por radiación. Dolores severos ocurrieron en 80 por ciento de los pacientes con tumores pero solamente 19 por ciento de pacientes con lesiones por radiación. El tronco bajo [C7 - 8 T1] estaban envueltos en el 72 por ciento de los tumores, y 32 por ciento también tenían tumores epidurales. 78 por ciento de las lesiones por radiación afectaron

el plexo superior [C5 - 6]. El Horner Syndrome era más común en tumores y linfedema en lesiones por radiación. El tiempo de RT y los síntomas del plexo y la dosis de RT también eran diferentes. Por síntomas dentro de un año de RT, las dosis que excedían de 6,000 R estaban asociados a daño por radiación en áreas donde se aplicaron dosis baja estaba asociado con infiltración. Por lo tanto dolores de las lesiones del tronco superior con linfedema sugiere lesiones por radiación y lesiones en el tronco bajo con Horner syndrome implica infiltración de tumor.

(Sometido por Ramón E. Ortiz Domenech, MD)

C U R S O S

TITLE OF PROGRAM: "Emergencies in Internal Medicine, V: Critical Decision Making in Patient Management"

DATES: November 30-December 4, 1981

LOCATION: Condado Holiday Inn Resort, San Juan, Puerto Rico

FEE: \$310 Physicians in Practice: \$210 Physicians in Training

CME CREDIT HOURS: 35, Category 1, A.M.A. American College of Emergency Physicians and American Academy of Family Practice approval requested. (24 hrs. lectures; 11 hours optional workshops)

MEDICAL SPECIALTY OR SPECIALTIES PROGRAM IS DESIGNED FOR: Internal Medicine, General Practice, Emergency Medicine and Physicians in Training

REGISTRATION: Advance registration requested. Registration will be accepted at time of meeting.

SPONSOR: University of Miami School of Medicine, Department of Medicine, Division of General Medicine

COSPONSOR: Veterans Administration Medical Center, Department of Medicine, San Juan, Puerto Rico

PROGRAM FORMAT: Lectures, small group workshops utilizing pre-constructed patient-management problems (some workshops to be given in English and Spanish); self-evaluation tests; open discussion; printed test.

FOR INFORMATION/REGISTRATION, CONTACT: Division of Continuing Medical Education D23-3, Uni-

versity of Miami School of Medicine, P. O. Box p16960, Miami, FL 33101. Tel. Area Code: 305 547-6716.

1982 REGIONAL CME MEETINGS - AMERICAN COLLEGE OF PHYSICIANS

JUN 24, Mexico: Mexico City, Mexico. **INFO:** Luis Landa, MD, FACP, Sierra Leona 230, Mexico City, Mexico 10, DF, MEXICO.

SEP 10-12, Ohio: Daytonian Inn, Dayton, OH. **INFO:** Richard G. Farmer, MD, FACP, Cleveland Clinic, 9500 Euclid, Cleveland, OH 44106.

SEP 11-12, South Dakota: Alex Johnson Hotel, Rapid City, SD. **INFO:** Reuben J. A. Bareis, MD, FACP, PO Box 3115, 2800 Jackson Blvd., Rapid City, SD 57701.

SEP 11-12, Wisconsin: La Crosse, WI. **INFO:** Charles L. Junkerman, MD, FACP, 831 N. 66th St., Wauwatosa, WI 53213.

SEP 19-20, Illinois: Drake Hotel, Chicago, IL. **INFO:** Rolf M. Gunnar, MD, FACP, Loyola University Medical Center, 2160 S. First Ave., Maywood, IL 60153.

SEP 25-26, Montana: Colonial Inn, Helena, MT. **INFO:** William A. Reynolds, MD, FACP, Western Montana Clinic, Box 1307, Missoula, MT 59801.

SEP 25-26, Washington: Davenport Hotel, Spokane, WA. **INFO:** Marvin Turck, MD, FACP, Dept. of Medicine, Harborview Medical Center, 325 Ninth Ave.,

Seattle WA 98104.

SEP 25-27, Eastern Pennsylvania: Pocono Hershey Resort, White Haven, PA. INFO: James E. Clark, MD, FACP, Chief, Dept. of Medicine, Crozer-Chester Medical Center, 15th Street and Upland Ave., Chester, PA 19013.

OCT 2-3, Arkansas: University of Arkansas for Medical Sciences, Little Rock, AR. INFO: James E. Doherty, III, MD, FACP 300 E. Roosevelt Rd., Little Rock, AR 72206.

OCT 8-11, Michigan: Boyne Highlands, Harbor Springs, MI. INFO: Boy Frame, MD, FACP 543 Lakepointe, Grosse Pointe Park, MI 48230.

OCT 9, Utah: Salt Lake Hilton, Salt Lake City, UT. INFO: John H. Holbrook, MD, FACP, 2797 Commonwealth Ave., Salt Lake City, UT 84109.

OCT 9-10, Idaho: Anderson Center, Boise, ID. INFO: Charles D. Steuart, MD, FACP, 848 La Cassia Dr., Boise, ID 83705.

OCT 10, Maryland: University of Maryland School of Medicine, Baltimore, MD. INFO: Albert I. Mendeloff, MD, FACP, Sinai Hospital of Baltimore, 2401 W. Belvedere Ave., Baltimore, MD 21215.

OCT 16, Western Canada (Alberta, Saskatchewan, British Columbia): Banff Springs Hotel, Banff, Alberta. INFO: Brian J. Sproule, MD, FACP, 6-104 Clinical Sciences Bldg., University of Alberta, Edmonton, AB T6G 2G3, CANADA.

OCT 15-16, Upstate New York: Holiday Inn/University Area-DWTN, NY. INFO: Paul F. Griner, MD, FACP, University of Rochester Medical Center, 260 Crittenden Blvd., Rochester, NY 14620.

OCT 15-17, Missouri: Almedea Plaza Hotel, Kansas City, MO. INFO: Davis M. Kipnis, MD, FACP, Dept. of Medicine, Washington University School of Medicine, 660 S. Euclid, St. Louis, MO 63110.

OCT 16, Ontario: Donald Gordon Center, Kingston, ON. INFO: Robert Volpe, MD, FACP, Wellesley Hospital-Medical Dept., 160 Wellesley St. East, Toronto, ON M4Y 1J3, CANADA.

OCT 16-17, Puerto Rico: Dorado Beach Hotel, PR. INFO: Russell A. Del Toro, MD, FACP, PO Box 13158, Santurce, P. R. 00908.

OCT 17, Kentucky: Hyatt Regency Hotel, Lexington, KY. INFO: Walter S. Coe, MD, FACP, 207 Baptist E. Doctors Bldg., Louisville, KY 40207.

OCT 16-18, Florida: Sonesta Beach Hotel, Key Biscayne, FL. INFO: Roy H. Behnke, MD, FACP, College of Medicine, University of South Florida, 12901 North 30th St. Tampa, FL 33612.

OCT 23-24, WPA/WVA: West Virginia Medical Center, Morgantown, WV. INFO: Stanley R. Shane, MD, FACP, Dept. of Medicine, West Virginia University Medical Center, Morgantown, WV 26505.

OCT 29-31, Tennessee: Nashville, TN. INFO: Clifton R. Cleaveland, MD, FACP, 1000 Signal Mountain Blvd., Signal Mountain TN 37377.

OCT 30-31, New England: Sheraton, Boston, MA. INFO: James E. Dalen, MD, FACP, Dept. of Cardiovascular Medicine, University of Massachusetts Medical Center, Worcester, MA 01605.

OCT, Minnesota: Rochester MN. INFO: John A. Spittell, Jr., MD, FACP, Mayo Clinic, 200 First St. SW, Rochester, MN 55901.

OCT, Nevada: Reno, NV. INFO: Robert J. Barnett, MD, FACP, 166 Greenridge Dr., Reno, NV 89509.

NOV 5-7, Oklahoma: Shangri-la, Afton, OK. INFO: Solomon Papper, MD, FACP, University Hospital, PO Box 25606 - Room 310B, Oklahoma City, OK 73125.

NOV 13-14, Arizona: Doubletree Inn, Tucson, AZ. INFO: Alan L. Gordon, MD, FACP, 2200 N. Third

St., Phoenix, AZ 85004.

NOV 20, Indiana: Hilton Hotel, Indianapolis, IN.
INFO: Walter J. Daly, MD, FACP, Indiana University Medical Center, Emerson Hall, Room 317, 1100 W. Michigan St., Indianapolis, IN 46223.

NOV 20, New Jersey: Meadowlands Hilton Hotel, Secaucus, NJ. INFO: Michael Bernstein, MD, FACP, Overlook Hospital, 193 Morris Ave., Summit, NJ 07901.

NOV 20-21, Georgia: Omni International Hotel, Atlan-

ta, GA. INFO: William C. Waters, III, MD, FACP, 35 Collier Rd. NW, Suite 350, Atlanta, GA 30309.

DEC 3-4, Texas: Galleria Plaza Hotel, Houston, TX.
INFO: L. Rodney Rodgers, MD, FACP, Hermann Professional Bldg., Suite 1232, Houston, TX 77030.


DEC 11-12, New Mexico: Education Center, VA Hospital, Albuquerque, NM. INFO: Ulton G. Hodgins, Jr., MD, FACP, Suite 372, Winrock Medical Plaza NE, Albuquerque, NM 87110.



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Use in ambulatory patients: Empirin with Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system (CNS) depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with Empirin with Codeine may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Use in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Empirin with Codeine should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS:

Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Empirin with Codeine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Allergic: Precautions should be taken in administering salicylates to persons with known allergies; patients with nasal polyps are more likely to be hypersensitive to aspirin.

Special risk patients: Empirin with Codeine should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture, peptic ulcer, or coagulation disorders.

ADVERSE REACTIONS: The most frequently observed adverse reactions to codeine include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, and pruritus.

The most frequently observed reactions to aspirin include headache, vertigo, ringing in the ears, mental confusion, drowsiness, sweating, thirst, nausea, and vomiting. Occasional patients experience gastric irritation and bleeding with aspirin. Some patients are unable to take salicylates without developing nausea and vomiting. Hypersensitivity may be manifested by a skin rash or even an anaphylactic reaction. With these exceptions, most of the side effects occur after repeated administration of large doses.

DOSEAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. Empirin with Codeine is given orally. The usual adult dose for Empirin with Codeine No. 2 and No. 3 is one or two tablets every four hours as required. The usual adult dose for Empirin with Codeine No. 4 is one tablet every four hours as required.

DRUG INTERACTIONS: The CNS depressant effects of Empirin with Codeine may be additive with that of other CNS depressants. See WARNINGS.



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Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Breast Feeding Best For Healthy Infants

Infants' Diets Set

An individual grows faster during the first year of life than during any other time. Birth weight usually triples in a year. This growth is made possible by adequate amounts of calories and nutrients.

Breast-feeding is recommended for most infants, says a pamphlet from the American Medical Association. During the early months of life, human milk is the preferred source of nutrients, and it may provide the infant with other health advantages. Nutritionally complete infant formulas are available for use when it is not possible for the mother to breast feed. If vitamin or mineral supplements are needed, the doctor will prescribe them.

Between ages 4 to 6 months, most infants are ready to begin eating very small amounts of semisolid foods. After 6 months of age, a milk diet cannot satisfy all of the infant's needs. Iron-enriched cereals are added, followed gradu-

ally by pureed vegetables, fruits, and meats. Milk, however, will continue to be the most important food until the infant is 1 year old.

If breast feeding is discontinued before 6 months of age, it is best for the infant to have an iron-fortified formula. Infants are vulnerable to iron deficiency once they have used the stored iron that they have at birth. Their diets should include good sources of iron: egg yolk, green vegetables, meats, and iron-enriched products.

By 1 year of age, most infants are eating a variety of chopped solid foods and drinking fresh cow's milk. Their appetites and enthusiasm about foods may fluctuate, but many new foods, introduced one at a time and in small amounts, are usually well accepted.

Children need three good meals a day plus snacks, especially if they are very active. Snacks should be small servings of the same nutritious foods needed at mealtime, such as fruits, juices, milk, crackers with peanut butter or cheese, small sandwiches, raw vegetables, nuts, or cereals.

Poor appetites are fairly common among preschool children. The refusal to eat period is a difficult time for parents, but there is usually no cause for concern unless the problem persists.



December, 1980
Frank Chappell
Science News Editor
AMA

NOTICIAS

AMA NEWS:

CHLAMYDIA TRIGGERS NEW EPIDEMIC OF SEXUALLY TRANSMITTED DISEASE

CHICAGO - The same tiny organism that causes trachoma and blindness in much of the Third World is now behind a soaring new epidemic of sexually transmitted disease in the United States.

The offender is known to medicine as Chlamydia. It is not exactly a bacterium, but is not a virus either. It is just chlamydia, and it infects many more persons than does gonorrhea, says King K. Holmes, M. D., of the University of Washington School of Medicine and the U. S. Public Health Service Hospital, Seattle.

In the United States, chlamydia infection is probably about three times as common as gonorrhea among men in many communities, including Seattle, Dr. Holmes says. In the prenatal clinic at the University of Washington, doctors have found chlamydial infection in 5 to 10 percent of all women. Only about 1 percent have gonorrhea.

In an interview in the May 1 Journal of the American Medical Association conducted by Lawrence D. Grouse, M. D., a senior editor of the Journal, Dr. Holmes points out that chlamydial infections are epidemic in this country, yet they are neither well recognized nor correctly treated in many instances.

Nationally there has been an "alarming increase" in the number of cases of ectopic pregnancy (malplaced fetus) and salpingitis (inflammation of the uterine tube), he points out. Each ectopic pregnancy represents one fetal death.

In expectant mothers the disease is particularly serious, in that it can lead to pneumonia or eye infection in the newborn infant. These mothers also are more likely to have miscarriages or stillbirths.

Treatment is with tetracyclines and sulfona-

mides, which can be effective against chlamydia, but treatment on an out-patient basis has had an unacceptably high failure rate, and many of the victims should be hospitalized for controlled treatment, he says.

Worldwide, the main problem brought by chlamydia has been trachoma. In the United States, genital infections in adults have caused the greatest concerns. Recently there has been emphasis on the impact of the infection on newborns.

Dr. Holmes calls for "Greater awareness, diagnosis and treatment of chlamydial infections, as well as treatment of the sex partners of patients with chlamydial infections by practicing physicians" to begin to curb the epidemic.

SILICONE BAG BREAST IMPLANTS MAY BURST, TEXAS DOCTOR WARNS

CHICAGO — A warning to women who have received silicone-filled implants to enhance breast size — avoid a blow to the breast. The implanted bag may burst.

The June issue of an American Medical Association specialty journal reports on a case in Texas in which this happened. The released silicone moved through the body, up the shoulder and down into the arm, forming a hard, unsightly mass along the upper arm. Also the breast was deflated and smaller than its mate. Plastic surgery was required to remove the material and to replace the ruptured breast implant.

Writing in Archives of Dermatology, James Mason, MD, of the University of Texas Medical Branch,

Galveston, points out that use of silicone injections and implants for cosmetic purposes has been widespread for many years. Currently, it is used principally in implantable gel-filled bags.

Injection of liquid silicone is banned by the Food and Drug Administration because of the tendency to flow through the body away from the enhanced site, and cause cosmetic and health problems. It is this process that occurs when one of the implanted bags bursts.

Silicone used in the gel implants varies in consistency and cohesiveness, depending on the manufacturer, Dr. Mason says. Rupture of the gel-filled implants with subsequent diffusion of leaked silicone can be due to a relatively minor blow to the breast, he points out.

Usually the patient first notices that something is wrong when the breast suddenly becomes smaller, or notices a lump forming under the skin somewhere else in the body.

ETHICS POLICIES FOR DOCTORS STATED IN NEW AMA PUBLICATION

CHICAGO — Quality of life, allocation of health resources, illegal or excessive fees, confidentiality and informed consent are just part of the issues thoughtfully deliberated by the American Medical Association's Judicial Council in its new publication, *Current Opinions of the Judicial Council of the American Medical Association, 1981*.

Current Opinions relates to the revised Principles of Medical Ethics adopted by the AMA House of Delegates in 1980. *Current Opinions* "are not presented as the sole or only route to medical morality," according to the Judicial Council. *Current Opinions* supercedes all earlier publications of the Judicial Council.

Limited health care resources should be allocated efficiently and on the basis of fair, acceptable and humanitarian criteria, the Council states.

Priority should be given to persons who are most likely to be treated successfully or have long term benefit. Social worth is not an appropriate criterion.

The AMA declares positively that "A physician should not charge or collect an illegal or excessive fee. For example, an illegal fee occurs when a physician accepts an assignment as full payment for services rendered to a medicare patient and then bills the patient for an additional amount."

The Council states that informed consent is vital to the physician-patient relationship.

"The patient's right of self-decision can be effectively exercised only if the patient possesses enough information to enable an intelligent choice. The patient should make his own determination on treatment. Rational, informed patients should not be expected to act uniformly, even under similar circumstances, in agreeing to or refusing treatment."

In caring for defective infants, the Council declares, the advice and judgment of the physician should be readily available, but the decision whether to treat a severely defective infant and exert maximal efforts to sustain life should be the choice of the parents. The parents should be told the options, expected benefits, risks and limits of any proposed care; how the potential for human relationships is affected by the infant's condition, and relevant information and answers to their questions.

In coping with terminal illness, the Council says, the social commitment of the physician is to prolong life and relieve suffering. Where the observance of one conflicts with the other, the physician, patient, and/or family of the patient have discretion to resolve the conflict.

The booklet may be purchased from: Order Department OP-122, American Medical Association, P. O. Box 821, Monroe, Wis. 53566. Single copies are \$4.00.

NEW TREATMENT METHODS SAVING SICKLE CELL CHILDREN

CHICAGO — Progress in treatment techniques can save lives of children with sickle cell anemia, says a report in the May 8 Journal of the American Medical Association.

Pneumoniae infection has been the single greatest cause of death for children with sickle cell anemia in the first five years of life. The infection progresses to meningitis and death unless it is treated promptly and effectively.

Darleen Powers, MD, of the Sickle Cell Center of Los Angeles County and University of Southern California School of Medicine, reports on experience in aggressive treatment of the infection crisis among children with the inherited blood defect.

In the California center, prior to July, 1972, of 23 sickle cell children who had pneumococcal septicemia (an infection that spreads into the blood), eight died and meningitis developed in 15. With new treatment techniques instituted at that time, the record changed dramatically. Since July, 1972, 11 children have had pneumococcal septicemia, but no children died and meningitis developed in only two.

"We believe that aggressive parental education regarding fever as an important sign of possible infection, coupled with a high index of suspicion, the ready availability of nursing staff, and the immediate institution of antibiotics, account for the observed successful outcome in the treatment of pneumococcal septicemia in sickle cell infants and children," Dr. Powers declares.

It is most important for parents to know that the child should be rushed to the treatment center at the first sign of fever. The pneumococcal disease may appear within four to eight hours after fever begins.

If the child survives to age six with sickle cell anemia, he or she usually is past the critical time, Dr. Powers says. Thus it is important for the parent to make contact with a sickle cell center as soon as the condition is discovered, and be prepared to take the child to the center immediately when fever develops.

The world around us gets noisier all the time. Airplanes above, trucks rumbling down the street or a neighbor's loud stereo are not only annoying, but when taken in high enough doses, they can cause emotional and physical health problems, particularly deafness. The American Medical Association says that not enough attention is given to the problem of noise as an environmental health hazard. It is estimated that more than six million workers in the United States are subjected to noise levels that are hazardous to hearing. One authority says that noise levels in this country increase by one decibel every year. And every day we are subjected to more noise than humans were even meant to hear. The damage from noise pollution is not apparent initially, but as exposure to high levels of noise decreases, hearing loss becomes noticeable. Many rock musicians, who hear their music at levels of 100 decibels or more, are partially deaf. In addition to hearing loss, loud noise also contributes to high blood pressure and stress and can adversely affect ulcers or heart disease — Jane Coughlin

HHS NEWS

CONFERENCE TO CONSIDER ECONOMIC, ETHICAL, SOCIAL ISSUES IN CORONARY ARTERY BYPASS SURGERY

An HHS-sponsored conference on the economic, social and ethical issues surrounding coronary artery bypass surgery is scheduled for April 21-23 in Washington, D. C.

The three-day technology assessment forum will examine effects of the surgery on quality of life and employment of the patients, legal issues, costs and cost effectiveness of the surgery and other questions. A previous conference, held last December, dealt with scientific and clinical aspects of the bypass procedure.

The conference is sponsored by the Natio-

nal Center for Health Care Technology with the collaboration of the National Heart, Lung and Blood Institute, both agencies of HHS.

In coronary artery bypass surgery, a blood vessel is removed from the patient's leg and sutured into the heart to bypass a blocked coronary artery and reestablish blood supply to the heart. More than 100,000 cardiac bypass procedures are performed each year.

The conference will be held at the Sheraton Washington Hotel. It is open to the public without charge.

Edward J. Brandt, MD, assistant secretary for health-designate, Department of Health and Human Services, will open the proceedings on Tuesday, April 21 at 8:30 a.m.

BOOKS REVIEW — FOREIGN TRAVEL & IMMUNIZATION GUIDE, 1980 edition, by Hans H. Neumann, MD, 64 pages, 5 1/2" x 8 1/2"; soft cover, \$4.50. Medical Economics Books, Box 157, Florence, Ky. 41042.*

Which immunizations for Kenya? Guatemala? Zanzibar? Doctors will find answers for patients who are planning trips in the new 1980 edition of *FOREIGN TRAVEL & IMMUNIZATION GUIDE*, just published by Medical Economics Books. The popular reference has been revised and updated to include the latest immunization requirements for visiting more than 200 countries and islands.

FOREIGN TRAVEL & IMMUNIZATION GUIDE also gives foreign travel health hints that doctors can pass on to their traveling patients—what to do about drinking water and swimming in the Soviet Union; how to find a doctor abroad; what to do about jet lag; and use of vitamins. Another section covers details of specific immunizations (dosage, reactions, effectiveness, and when they should be given).

This is the 9th edition of this concise, easy-to-use reference. Author Hans H. Neumann, MD, director of preventive medicine at the Department of Health in New Haven, Conn., has assembled data from the World Health Organization, the Center for Disease Control, from sources abroad, and from his personal travel experience. Written for both travelers and those who advise them, *FOREIGN TRAVEL & IMMUNIZATION GUIDE* is a valuable source of helpful information for preventing illness while traveling and assuring more pleasant foreign trips.

In Hypertension*...When You Need to Conserve K⁺

Every Step of the Way



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K⁺ supplement or K⁺-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K⁺ supplement or K⁺-sparing agent).

Serum K⁺ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. The following is a brief summary.

* WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and tri-

amterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K⁺ frequently, both can cause K⁺ retention and elevated serum K⁺. Two deaths have been reported with such concomitant therapy (in one recommended dosage was exceeded in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both; hyperglycemia and glycosuria (diabetic insulin requirements may be altered); hyperuricemia and gout; digitalis intoxication (in hypokalemia); decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted

cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of Dyazide, although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules. Single Unit Packages (unit-dose) of 100 (intended for institutional use only) in Patient-Pak™ unit-of-use bottles of 100.

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SK&F CO.
a SmithKline company
Carolina PR 00630

Motrin[®] vs aspirin w/codeine...

(ibuprofen)

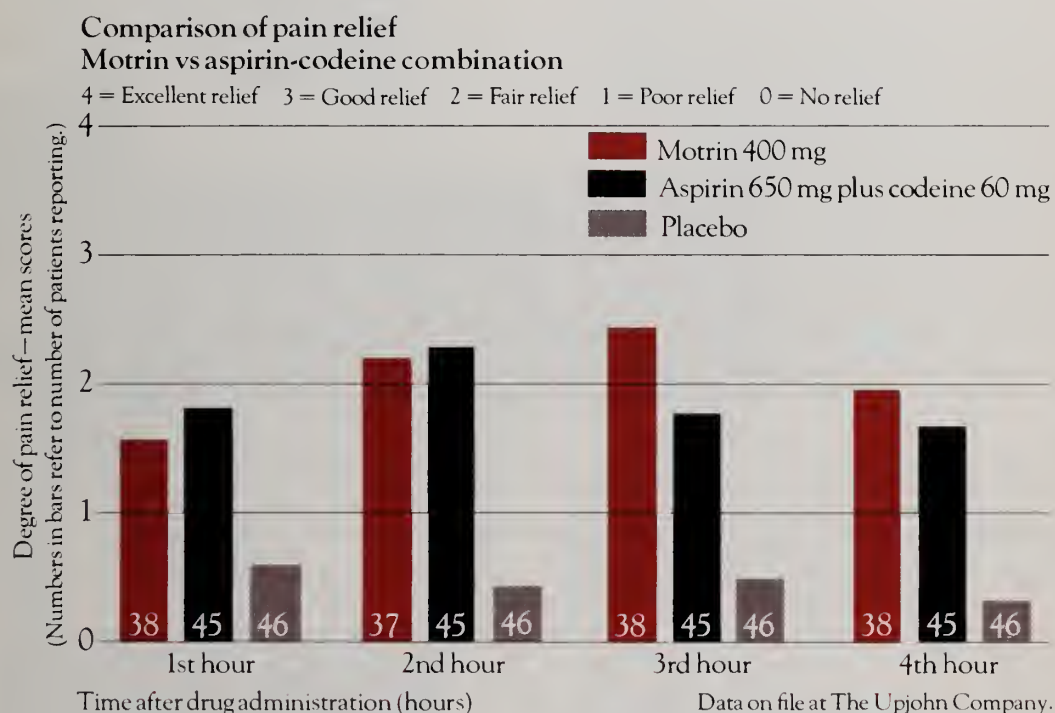


compare the analgesic effect

A *Motrin* 400 mg dose relieved postsurgical dental pain as effectively as a combination of 650 mg aspirin and 60 mg codeine (two aspirin-with-codeine No. 3 tablets) in a study of 129 patients.

In this double-blind, placebo-controlled, randomized study, no statistically significant difference in relief of pain was noted at 1, 2, and 4 hours between the *Motrin* and aspirin-with-codeine groups... with *Motrin* being significantly more effective ($p = 0.03$) at the three-hour interval.

Active treatment was significantly more effective ($p < 0.0001$) than placebo at all time intervals.



One tablet q4-6h prn

For relief of mild to moderate pain:

Motrin[®] 400mg TABLETS
ibuprofen, Upjohn

- Not a narcotic • Not addictive • Not habit forming • Nonscheduled
- Acts peripherally • Relieves pain rapidly • Relieves inflammation • Indicated in acute and chronic pain • Well tolerated (The most common side effect with *Motrin* is mild gastrointestinal disturbance.)

Please turn the page for a brief summary of prescribing information.

Upjohn

Motrin[®] (ibuprofen)

now proved an effective analgesic for mild to moderate pain

Motrin[™] Tablets (ibuprofen, Upjohn)

Indications and Usage: Relief of mild to moderate pain.

Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin:* Used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy nor by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness,* headache,* nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis, including flares of chronic disease: Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for relief of pain.

Do not exceed 2400 mg per day.

Caution: Federal law prohibits dispensing without prescription.

For additional product information, see your Upjohn representative or consult the package insert.

Send now for the only book on crime ever written by a dog!

Get hot tips on crime prevention from the Crime Dog himself! Me! Send for my book. It's got all the hit topics like: how to burglarproof your home, how not to get mugged, and more!

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this publication and The Ad Council.

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Upjohn

THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

MED B-4-S

BactrimTM (trimethoprim and sulfamethoxazole) succeeds

Bactrim is useful for the following infections when due to susceptible strains of indicated organisms (see indications section in summary of product information):

Expanding its usefulness in antimicrobial therapy



in recurrent UTI...
a continuing record of high clinical effectiveness against common uropathogens

in acute otitis media in children...
effective against both major otic pathogens...with *b.i.d.* convenience

in acute exacerbations of chronic bronchitis in adults...
clears the sputum and lowers its volume...on *b.i.d.* dosage

in shigellosis...
faster relief of diarrhea than with ampicillin²

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. Note: The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. Limited clinical information presently available on effectiveness of treatment of otitis media with Bactrim when infection is due to penicillin-resistant *Haemophilus influenzae*. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonia. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β -hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: General: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. **Blood dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. **Allergic reactions:** Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. **Gastrointestinal reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. **CNS reactions:** Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

Miscellaneous reactions: Drug fever, chills, toxic nephrosis with oliguria and anuria, periarthritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) *b.i.d.* for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:

Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) *b.i.d.* for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS:

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: Double Strength (DS) tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose[®] packages of 100. Prescription Paks of 20 and 28. Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose[®] packages of 100; Prescription Paks of 40. Pediatric Suspension, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry-flavored—bottles of 100 ml and 16 oz (1 pint).

Suspension, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).



ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

BactrimTM succeeds

in recurrent urinary tract infections*



from site to source

Bactrim continues to demonstrate high clinical effectiveness in recurrent urinary tract infections. Bactrim reaches effective levels in urine, serum, and renal tissue¹...the trimethoprim component diffuses into vaginal secretions in bactericidal concentrations¹... and in the fecal flora, Bactrim effectively suppresses Enterobacteriaceae^{1,2} with little resulting emergence of resistant organisms.

1. Rubin RH, Swartz MN: *N Engl J Med* 303 426-432 Aug 21, 1980. 2. Data on file, Medical Department, Hoffmann-La Roche Inc.

BactrimTM DS

160 mg trimethoprim and 800 mg sulfamethoxazole

DOUBLE STRENGTH TABLETS

maximizes results with B.I.D. convenience



* due to susceptible strains of indicated organisms

Please see previous page for summary of product information.



BOLETIN

ASOCIACION MEDICA DE PUERTORICO

CONTENIDO:

EDITORIAL: THE DETECTION OF STAGE I CARCINOMA OF THE LUNG

TOXOPLASMOSIS SEROLOGIC SURVEY IN PUERTO RICO:
A STUDY OF A NORMAL POPULATION AND CHRONIC RENAL PATIENTS

DIPHThERIA: SEROLOGIC STUDY OF 422 PERSONS IN PUERTO RICO

ABNORMAL HEMOGLOBINS DETECTED IN SCREENING OF
PUERTO RICAN POPULATION

HEPATITIS VIRAL: ESTUDIO SEROLOGICO EN PUERTO RICO.
REVISION Y REPASO DE LA LITERATURA – 1981

CASOS DE ELECTROCARDIOGRAFIA PEDIATRICA

ELECTROCARDIOGRAM OF THE MONTH

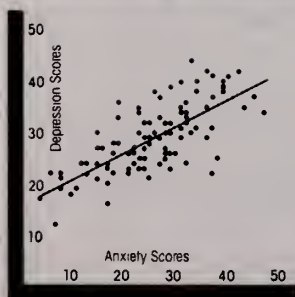
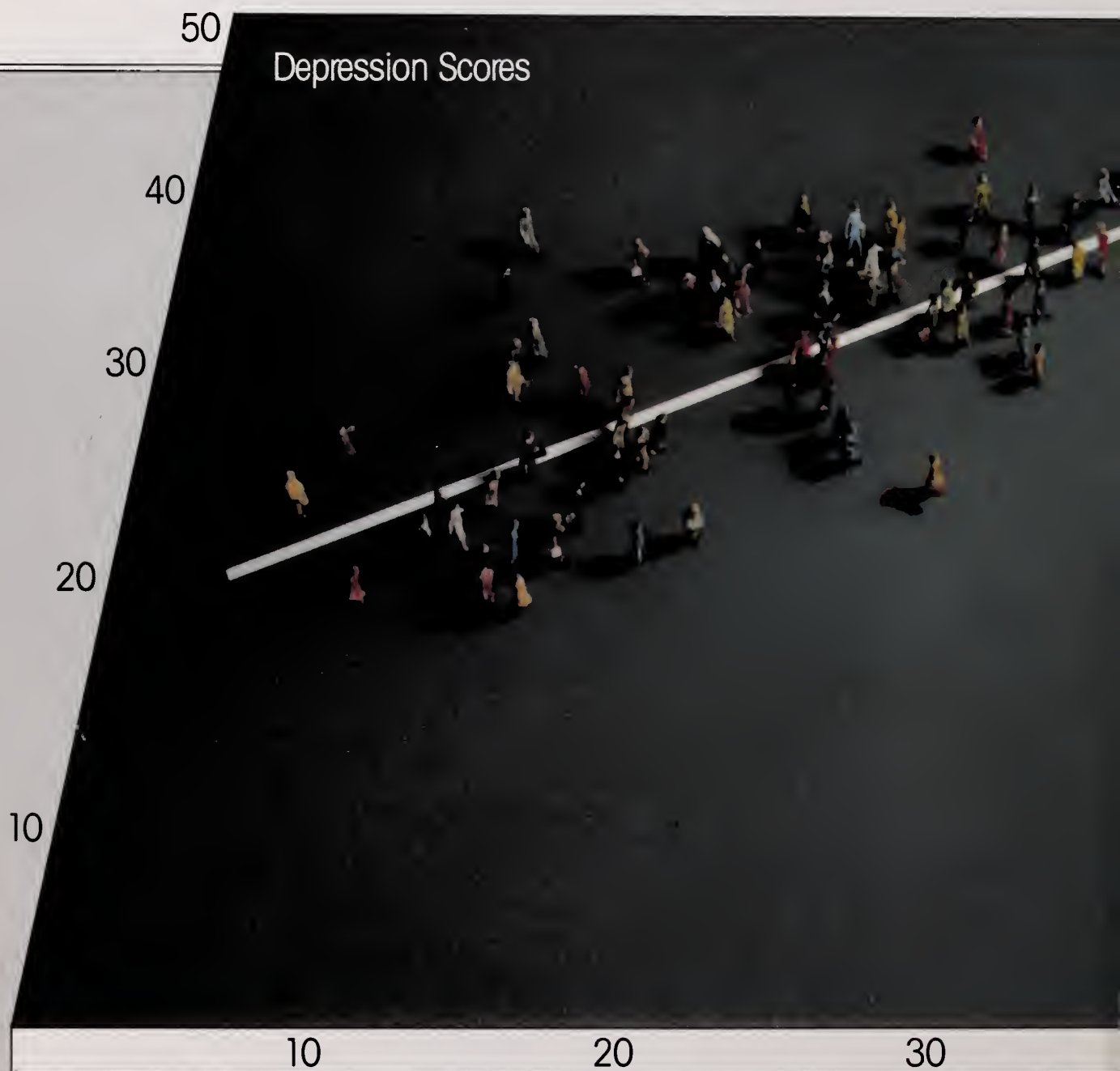
GRAPHICS

ABSTRACTOS DE LITERATURA MEDICA

CURSOS – NOTICIAS

INDICE PAGINA 260

FOR THE 7 OF 10 NONPSYCHOTIC



Clear correlation between anxiety and depression³

The above graph illustrates a relationship between anxiety and depression, indicating that patients seldom present with anxiety or depression alone; more often they have both in varying degrees. Data based on a sampling of 100 outpatients (64 male; 36 female) seen at a general psychiatric clinic.

³Adapted from Claghorn, J. The anxiety-depression syndrome. *Psychosomatics* 11:438-441, Sept-Oct 1970.

DEPRESSED PATIENTS WHO ARE ALSO ANXIOUS^{1,2}

Most depressed patients are also anxious. . .

Some authors estimate that 70% of all nonpsychotic patients with symptoms of depression have concomitant symptoms of anxiety.^{1,2} One author found a distinct correlation between anxiety and depression scores in 100 nonpsychotic outpatients administered the Minnesota Multiphasic Personality Inventory in a general psychiatric clinic.³ As depression scores increased, so did anxiety scores. No attempt was made to select patients other than to exclude psychotics.

but not psychotic

The logic of treating both components of anxious depression is clear. Antipsychotics, like the phenothiazines, however, carry a well-documented risk of tardive dyskinesia.⁴ Because of this, an APA Task Force recently recommended the judicious use of phenothiazines in cases other than chronic psychosis or the use of alternative treatments.

A better way to give relief

Limbitrol combines the specific anxiolytic action of Librium® (chlordiazepoxide HCl/Roche)—a benzodiazepine with a long history of safe use—with the antidepressant action of amitriptyline, a tricyclic of established clinical efficacy. In comparison to phenothiazines, Limbitrol and its components have rarely been associated with tardive dyskinesia or other extrapyramidal side effects. And in terms of rapid response and patient compliance, Limbitrol appears to be superior to amitriptyline alone. Controlled multiclinic studies showed Limbitrol relieved more symptoms more rapidly than did amitriptyline.⁵ Despite a higher incidence of drowsiness, the dropout rate due to side effects was lower with Limbitrol. (See adverse reactions section in summary of product information on next page. As with any CNS-acting agent, patients should be cautioned about driving or using dangerous machines while on therapy with Limbitrol.)

References: 1. Rickels K: Drug treatment of anxiety, in *Psychopharmacology in the Practice of Medicine*, ed. Jorvik ME. New York, Appleton-Century-Crofts, 1977, p. 316. 2. Schotzberg AF, Cole JO: Benzodiazepines in depressive disorders. *Arch Gen Psychiatry* 35:1359-1365, 1978. 3. Claghorn J: The anxiety-depression syndrome. *Psychosomatics* 11:438-441, 1970. 4. The Task Force on Late Neurological Effects of Antipsychotic Drugs: Tardive dyskinesia, summary of a task force report of the American Psychiatric Association. *Am J Psychiatry* 137:1163-1172, 1980. 5. Feighner JP *et al*: A placebo-controlled multicenter trial of Limbitrol versus its components (amitriptyline and chlordiazepoxide) in the symptomatic treatment of depressive illness. *Psychopharmacology* 61:217-225, 1979.

Anxiety Scores

50

In moderate depression and anxiety

Limbitrol®[®]

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Relief without a phenothiazine

Please see summary of product information on next page.

LIMBITROL® TABLETS Tranquillizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety.

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated. Sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12.

In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly. Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10, Prescription Paks of 50.



Lung cancer is now an equal opportunity tragedy.

Remember when lung cancer was a man's disease. Because men had been smoking longer than women. But the women's smoking boom that started in the 1930's and 40's—is paying most cruel dividends today. Yet most people still think lung cancer is a man's disease. Tell your female patients the true story. That lung cancer is now an equal opportunity tragedy. That's what "you've come a long way, baby" is all about.

ROCHE

ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Office on Smoking and Health
Public Health Service Rockville, MD 28057

Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Eye Glasses Aid Millions to See

Glasses Aid Vision

By far the most commonly used medical device in the world today is prescription eyeglasses. There are relatively few individuals who do not need glasses at least part of the time at some time during life.

Prescription eyeglasses, including contact lenses, are used for the correction of refractive errors. The main function of glasses is to help focus rays of light on the retina. Improperly fitted glasses will not damage the eye, but they can cause headache, nausea, eye fatigue, blurred vision and irritation, says a booklet from the American Medical Association.

Tinted glasses and sunglasses only cut down on glare from light, and, unless they are also corrective lenses, have no effect on vision. It is best to limit use of tinted glasses to the beach, snowy areas, and to use

when driving over concrete highways in bright light.

Contact lenses are growing more popular and seem to benefit some people more than others. Unlike glasses, improperly fitted contacts can irritate the cornea and cause serious eye problems.

Two types of contact lenses are now available: hard and soft. Soft lenses for some are more comfortable. They easily conform to the shape of the cornea, absorb moisture from the eye and keep foreign matter away because they cover a large surface of the eye. They are less likely to fall out than are hard lenses.

But soft contacts often give a less crisp image, are more difficult to clean and are more expensive. Some eye conditions rule out their use entirely and others are not helped by them.

Some ophthalmologists are worried that the soft lenses may more easily become contaminated with bacteria and cause infection, or that they may absorb chemicals that could injure the eyes. Pregnant women have been advised not to wear soft contacts, as sufficient testing to rule out danger to the fetus has not been done, the AMA booklet says.



November, 1980
Frank Chappell
Science News Editor
AMA

MINIPRESS[®] Effectively (prazosin HCl) by Reducing



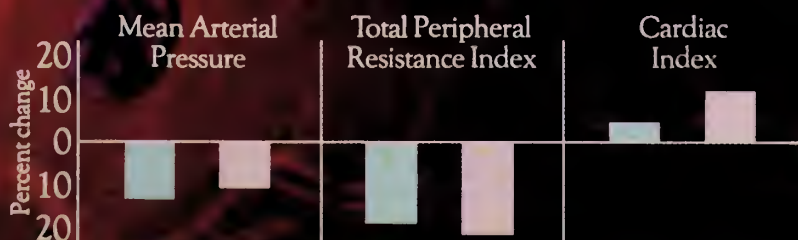
Artist's representation of the lumen of an arteriole, dilation of which results in reduced peripheral resistance and blood pressure.

Controls Hypertension Peripheral Resistance



- MINIPRESS Reduces Mean Arterial Pressure
- MINIPRESS Reduces Total Peripheral Resistance
- MINIPRESS Does Not Reduce Cardiac Index

...and Maintains These Effects Over the Long Term



Relative hemodynamic changes at rest and during exercise after one year of prazosin therapy in 10 hypertensive patients. Adapted from Lund-Johansen¹

■ Rest ■ Exercise

MINIPRESS[®]

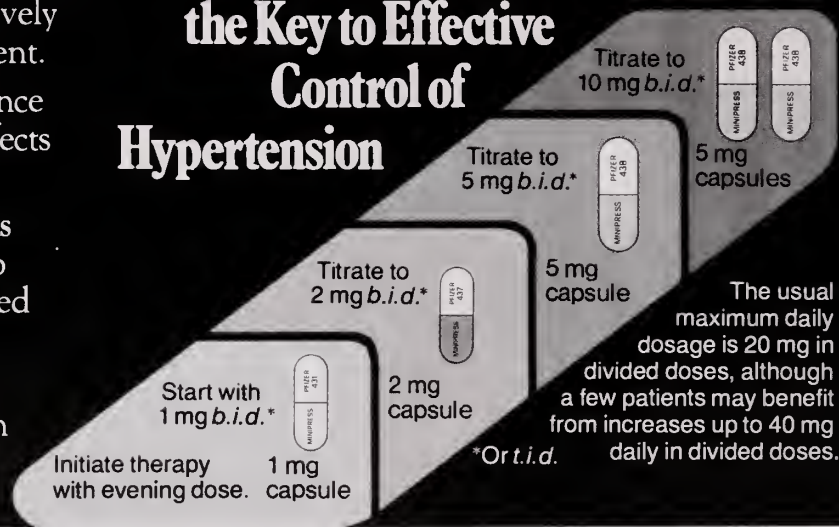
(prazosin HCl) Capsules 1 mg,
2 mg, 5 mg

MINIPRESS®

(prazosin HCl) Capsules 1 mg,
2 mg, 5 mg

- Effectively lowers elevated blood pressure by reducing peripheral resistance.
- Maintains cardiac output which allows patients to maintain an active life style.
- Maintains renal blood flow and glomerular filtration rate so it can be used effectively even in patients with renal impairment.
- Not a CNS agent so patients experience few of the troublesome CNS side effects that impair their quality of life.
- Cardiovascular response to exercise is preserved so patients are less likely to experience the fatigue often associated with beta-blocker therapy.
- A small percentage of patients have experienced orthostatic hypotension and syncope.

B.I.D. Dosage Titration... the Key to Effective Control of Hypertension



BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) CAPSULES For Oral Use

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, rhinitis, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Reference:

1. Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in *Prazosin Clinical Symposium Proceedings*, published as a special report by Postgrad Med. New York, McGraw-Hill Book & Education Services Group, 1975, pp 45-52.



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PFIZER INC

BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

(USPS-060000)

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Fundado en 1903

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VOLUMEN 73

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Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Little Strokes Can Curb Capacities

Strokes Cause Ills

An often unsuspected cause of mental and physical incapacity is a series of "little strokes."

A stroke occurs when the blood supply to a part of the brain is reduced or cut off. This can be caused by a blood clot or by hemorrhage — bleeding from an artery in the brain. When the nerve cells of a part of the brain are deprived of their blood supply, the part of the body controlled by these nerve centers cannot function normally.

Little strokes may start when a person is in the 30s or 40s, striking silently at night, or passing almost unnoticed as a sudden dizzy spell, a momentary blackout, or just a few moments of confusion. The stroke itself is not severe enough to compel the patient to seek medical aid, but some permanent brain damage remains just the same.

The American Medical Association points out that a formerly kind, gentle person may become highly impatient and irritable. Judgment is often impaired. A strong man may become weak and prone to tears. Suspiciousness is common. Some become sloppy in dress and befuddled in thought, others lose a part of their moral sense. Sometimes the sufferer loses interest in family and friends, lives secretly, constantly hiding things that he cannot find later.

When the symptoms are mild, as they often are, the person may get along fairly well. Surveys show that a sufferer from little strokes can get along better in the slower-going farm and small-town areas than in the faster-living city.

The problem of small strokes is one of the most difficult ever tackled by medical science. The most hopeful research approach is that of finding means to prevent stroke. Science seeks to learn more about how to recognize early symptoms so that treatment can be instituted promptly.



July, 1981
Frank Chappell
Science News Editor
AMA

DUAL PROBLEM

A photograph of a middle-aged man in a laboratory or clinical setting. He is shirtless, wearing light-colored shorts, and is leaning forward with his right hand on his lower back, indicating pain. Two thin white lines originate from the top of the frame and point to the words 'pain' and 'spasm' in the text overlay. The background shows laboratory equipment and shelves with various bottles.

**pain
spasm***

DUAL THERAPY

an analgesic + muscle spasm relaxation

PARAFON FORTE provides
the effective pain relief of
TYLENOL® acetaminophen

PARAFON FORTE also provides
the muscle spasm relaxation
of chlorzoxazone.

PARAFON FORTE® tablets

(chlorzoxazone 250 mg plus acetaminophen 300 mg)

Summary of Prescribing Information

***Indications:** Based on a review of this drug by the National Academy of Sciences-National Research Council and / or other information, FDA has classified the indications as follows:

"Probably" effective as an adjunct to rest and physical therapy for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Chlorzoxazone does not directly relax tense skeletal muscles in man.

Contraindications: Sensitivity to either component

Warnings: Usage in Pregnancy—Use in women of childbearing potential only when potential benefits outweigh possible risks

Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped

Adverse Reactions: Occasionally, drowsiness, dizziness, lightheadedness, malaise, overstimulation or gastrointestinal disturbances may be noted. rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, chlorzoxazone may possibly have been associated with gastrointestinal bleeding. While PARAFLEX® (chlorzoxazone) tablets and other chlorzoxazone-

containing products have been suspected as being the cause of hepatic toxicity in approximately twenty-seven patients, it was not possible to state that the dysfunction was or was not drug induced.

Usual Adult Dosage: Two tablets q.i.d.

Supplied: Light green tablets, imprinted "McNEIL" and "PARAFON FORTE"—bottles of 100 and 500 18913

Caution: Federal law prohibits dispensing without prescription. Full directions for use should be read before administering or prescribing

For information on symptoms / treatment of overdosage, see full prescribing information.

PARAFON FORTE tablets are manufactured by McNeil Pharmaceutical, Dorado, PR 00646

LISTA DE ANUNCIANTES

BURROUGHS WELLCOME
Neosporin
Septra

JANSSEN PHARM.
Vermox

MC NEIL PHARM.
Haldol
Parafon Forte
Tolectin - DS
Tylenol w/Codeine

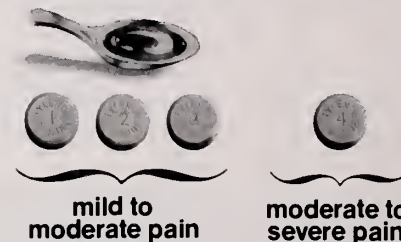
PFIZER CORPORATION
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Hygroton

TYLENOL[®] with Codeine

tablets  / elixir 



Summary of Prescribing Information

Description

Tablets: Contain codeine phosphate*: No. 1—7.5 mg ($\frac{1}{8}$ gr.); No. 2—15 mg ($\frac{1}{4}$ gr.); No. 3—30 mg ($\frac{1}{2}$ gr.); No. 4—60 mg (1 gr.)—plus acetaminophen 300 mg

Elixir: Each 5 ml. contains 12 mg. codeine phosphate* plus 120 mg. acetaminophen (alcohol 7%).

*Warning: May be habit forming.

Actions: Acetaminophen is an analgesic and antipyretic; codeine an analgesic and antitussive.

Contraindications: Hypersensitivity to acetaminophen or codeine.

Warnings: *Drug dependence:* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration, prescribe and administer with same caution appropriate to other oral narcotics. Subject to the Federal Controlled Substances Act.

Use in ambulatory patients: Caution patients that codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with this drug may exhibit additive CNS depression. When such a combination is contemplated, reduce the dose of one or both agents.

Use in pregnancy: Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Pediatric use: Safe dosage of this combination has not been established in children below the age of three.

Precautions: *Head injury and increased intracranial pressure:* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: Codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients: Administer with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: Most frequent: lightheadedness, dizziness, sedation, nausea and vomiting, more prominent in ambulatory than nonambulatory patients, some of these reactions may be alleviated if the patient lies down. Others: euphoria, dysphoria, constipation and pruritus.

Dosage and Administration: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. **TYLENOL with Codeine tablets** are given orally. The usual adult dose is, Tablets No. 1, No. 2, and No. 3 One or two tablets every four hours as required. Tablets No. 4 One tablet every four hours as required. **TYLENOL with Codeine elixir** is given orally. The usual doses are **Children (3 to 6 years):** 1 teaspoonful (5 ml.) 3 or 4 times daily; **(7 to 12 years):** 2 teaspoonful (10 ml.) 3 or 4 times daily; **(under 3 years):** safe dosage has not been established. **Adults:** 1 tablespoonful (15 ml.) every 4 hours as needed.

Drug Interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings. For information on symptoms/treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing.

TYLENOL with Codeine tablets are manufactured by McNeil Laboratories Co., Dorado, Puerto Rico 00646.

Caution: Federal law prohibits dispensing without prescription.

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08721

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McNeil Laboratories, McNEILAB, Inc.
Fort Washington, PA 19034

Sprains and Strains

Potent pain relief without aspirin complications



TYLENOL[®] with Codeine

tablets  / elixir 

Tablets Contain acetaminophen 300 mg plus codeine phosphate* as follows:
No.1—7.5 mg (1/8 gr); No.2—15 mg (1/4 gr); No.3—30 mg (1/2 gr); No.4—60 mg (1 gr)
Elixir Each 5 ml contains 12 mg codeine phosphate* plus 120 mg acetaminophen (Alcohol 7%)

*Warning: May be habit forming.

Would you fly a plane with no name?



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Hygroton® 25 ^{mg.} one a day

(chlorthalidone USP)

Because there is something in a name:
Confidence. Prescribe Hygroton by name
and make sure your patients receive what you
prescribe—write "Dispense as written" on
your Rx or sign in the appropriate place.

Hygroton®
(chlorthalidone USP)

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.
Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and

urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or

discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

USV
LABORATORIES

USV Laboratories Inc.
Manati, P.R. 00701

EDITORIAL



THE DETECTION OF STAGE I CARCINOMA OF THE LUNG

The problem of lung cancer in the United States at this time and its future projections are frightening. The 5 year survival has not improved significantly in the last few decades, and in the United States hovers around 8 percent for all stages and histologies. In Puerto Rico the 5 year survival is 5 percent. The projections are that by the year 1985 it will be the number 1 cancer killer in United States females and by the year 2000, over 300,000 patients will be diagnosed yearly in the United States as having cancer of the lung. Surgery, radiotherapy and chemotherapy have not significantly changed the 5 year survival for non-small carcinoma of the lung. Nevertheless, there are promising early results of multidrug chemotherapy on small cell carcinoma of the lung.

Those of us interested in Preventive Oncology have followed the evolving story of earlier detection of lung cancer very closely. Recently the American Cancer Society (A. C. S.) has published its guidelines for cancer related check-ups (1). After reviewing the data from randomized trials, the A. C. S. has changed its policy and does not recommend any test for the early detection of lung cancer in asymptomatic persons. The review is excellent (1), but I wish to go over some aspects and present to you the optimistic side of the problem.

The Philadelphia Pulmonary Research Project begun in 1951, screened 6,136 male volunteers, age 45 and over, with chest x-rays and questionnaires every 6 months (2). The lung cancers detected by screening had a 5 year survival of 13 percent. In this study, a chest x-ray every 6 months failed to significantly improve survival through earlier detection.

In 1971, the National Cancer Institute began sponsoring three randomized studies of lung cancer screening and its impact on mortality. The studies are being conducted at Johns Hopkins, Mayo Clinic and Memorial Hospital. The studies have slightly different designs, but all look at tri-annual sputum cytology and chest x-rays, and study its effect on lung cancer survival. The studies have shown that lung cancer can be detected earlier than by the usual methods, and at an earlier stage of evolution (3). The drawback, however, is that localization of "roentgenologically occult" lung cancer is often difficult. Nevertheless, mortality rates in the control and the experimental group are not significantly different (4).

In the study done at the Mayo Clinic (4), 4,500 high risk clinic patients were offered screening for lung cancer at 4-month intervals. Another 4,500 persons, also at high risk for lung cancer, who were used as controls, were followed with yearly chest x-rays and sputum cytology, the usual Mayo policy at that time. The Mayo lung project found that 48 percent of those screened at 4-month intervals were found to have post surgical stage I tumors. Stage I is defined as a tumor of less than 3 cm without any metastases, or with metastases to lymph nodes in the peri-bronchial and/or ipsilateral hilar region only. Also, tumors of more than 3 cm without metastases are considered stage I. As of December 31, 1979, they had observed 42 deaths due to lung cancer in the screened group, and 50 lung cancer deaths in the control group. This difference was not statistically significant. Mayo investigators found the most optimistic picture when squamous cell and adenocarcinoma patients were combined, with 13 deaths in the screened group, and 24 deaths in the control group. Nevertheless, the difference was also not statistically significant. Close to 30

percent of the diagnoses in this series were of small cell histology. The controls received more than the average surveillance given in many communities which may introduce a bias. The authors feel that the group with adenocarcinoma and squamous cell carcinoma histology, close to 50 percent of all lung cancers detected in this Mayo series, showed promising results (4).

The New York Lung Cancer Detection Program of Memorial Hospital diagnosed 269 lung cancers in 10,040 asymptomatic cigarette smoking men. Forty percent, 65 cases, were stage one at diagnosis, and their estimated probability of survival for "true pathologic" stage I cancer is 90 percent at 5 years. At Memorial Hospital, mediastinal lymph node dissection is performed in all cases treated by resection. So that for surgical stage I lung cancer, patients are proven free of mediastinal metastases microscopically. These are the cases that are considered "true pathologic" stage I lung cancer. The effect of screening on the survival of this population was estimated indirectly using the Kaplan-Meier estimate of survival probability (3). This was found to be 90 percent at 5 years for patients with "true pathologic" stage I lung cancer. These data from Memorial Hospital is the most hopeful.

In high risk patients, and for certain histologic types, earlier detection of lung cancer is still promising, but it has not been shown to improve 5 year survival. In selected groups, where cost is not a problem, sputum cytology and chest x-rays at 4-month intervals may still be the only alternative for heavy smokers.

To attain results similar to those achieved at Memorial, one needs access to good cytopathology, accurate fiberoptic bronchoscopic localization, skillfull lobectomy with mediastinal dissection, and meticulous pathologic study of margins and nodes.

Cost of the extensive work-up including cytology, x-rays, bronchoscopy, surgery and pathologic evaluation has been estimated to be about \$1,000 per patient (1). Furthermore, the massive work required to screen all smokers past age 45, estimated at about 20 million people, would be impractical and impossible with presently existing resources.

In summary, if you and your patients smoke, stop now. Prevention is the best way to cope with lung cancer. If you and your patient continue to smoke and develop symptomatic lung cancer, the chances are very high that both of you will die of the disease. This is so even if you have access to the best surgery, the best radiotherapy, and the best chemotherapy available at this time. Sputum cytology and chest x-rays every four months are costly, and impractical, and as yet have not been shown to affect the 5 year survival, although the Memorial Hospital survival projections are encouraging.

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TOXOPLASMOSIS SEROLOGIC SURVEY IN PUERTO RICO: A STUDY OF A NORMAL POPULATION AND CHRONIC RENAL PATIENTS

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Summary: Toxoplasmosis is an infection caused by protozoan *Toxoplasma gondii*. A serologic survey was conducted in 99 healthy subjects residing in the Metropolitan San Juan area and in 89 patients with chronic renal disease, including nine renal transplant recipients. A positive titer was considered a reaction of 1:16 or greater. The overall seropositivity of the healthy subjects was 63 percent of males and 52 percent of females. Over 80 percent of males or females older than 50 years had positive titers. Most of the subjects with positive serology (43/57) had titers of less than 1:256.

The percent of positive serology in chronic renal patients was lower than in healthy individuals (54 percent vs 63 percent) but the titers in those chronic renal patients with positive serology were higher, and over 60 percent had titers of 1:256 or higher.

Introduction

Toxoplasmosis is an infection caused by the obligate intracellular protozoan *Toxoplasma gon-*

dii. It is one of the most common infections in animals and man, it is an economically important cause of disease in animals and produces a variety of clinical manifestations in humans. Toxoplasmosis is a world wide zoonosis. The parasite is ubiquitous in nature and infects many animals but the most important group are members of the family Felidae, which appear to be the definite host in the life cycle (2). The two major routes of transmission of *T. gondii* to man are oral and congenital (3). Meat used for human consumption may contain tissue cysts, meat to man transmission has been documented with mutton, pork and goat meat. The evidence involving beef is tenuous. One of the most important modes of transmission is by handling kittens and their feces with oral contamination. There is no evidence of direct human to human transmission other than from mother to fetus. Evidence exists that acute toxoplasmosis in the mother infects about one third of the fetuses, but that chronic toxoplasmosis in the mother can lead to congenital toxoplasmosis, while it has been published seems to be very rare (1). Toxoplasmosis can also be transmitted by transfusions, organ transplantation (4), unpasteurized milk and raw eggs (3). The role of blood sucking arthropods has not been clearly defined (5).

There is an increasing prevalence of positive serologic reactions with increasing age with no significant difference between sexes. Toxoplasmosis is an increasingly important cause of morbidity and mortality in immunocompromised patients (6, 7). While the above has been consistently true, there is

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TABLE I
Serologic Survey of 99 Subjects for Toxoplasma Antibodies by IFA

Age Groups	Males			Females		
	Total Number	Number Pos.*	Percent Pos.	Total Number	Number Pos.	Percent Pos.
10-20	9	3	33	10	4	40
21-30	10	5	50	10	2	20
31-40	10	7	70	10	5	50
41-50	10	7	70	10	7	70
51-60	10	9	90	10	8	80
TOTAL	49	31	63	50	26	52

* A positive titer was considered a titer of 1:16 or greater.

very little data on the prevalence of positive toxoplasmosis serologic titers in Puerto Rico other than a study in which Dr. Méndez Cashion participated (11). The present study was designed to determine the prevalence of positive toxoplasmosis titers in Puerto Rico and also to determine the value of serology in the diagnosis of toxoplasmosis in the renal patient with fever.

Methods

Serum samples from normal subjects residing in the Metropolitan San Juan area were obtained from the Infectious Disease Research Laboratory serum bank. The group consisted of 99 subjects divided into four groups by age and sex, 49 males and 50 females, with an age range of 14 to 60 years old. Aliquots of serum samples from 89 patients with chronic renal disease were obtained from blood drawn for evaluation of other parameters. Eighty subjects were hemodialysis patients, nine were renal transplant patients with an age range of 25 to 83. Toxoplasma antibodies were determined by the Indirect Fluorescent Antibody Test, Electronucleonics Laboratories, Inc., Bethesda, Md.

Serial fourfold dilutions of the serum were prepa-

red in phosphate buffered saline (PBS) pH 7.6 (Na_2HPO_4 anhydrous 12.36pM, NaH_2PO_4 , H_2O 1.80pm, NaCl 85.0gm distilled water to a final volume of 1,000 ml). Successive dilutions of sera were placed in the slides containing toxoplasma antigen; placed in an incubator at 37°C for 30 minutes. The smears on the slides were then converted with fluorescein conjugated antihuman globulin. The slides are examined with the high-dry objective on a fluorescence microscope. Each time the test was performed controls for saline, negative serum and positive human serum of known titer were also carried out. The reaction is considered negative when the organisms fluoresce reddish-purple. The reaction in toxoplasma serology is positive when yellow-green fluorescence extends around the entire periphery of the organism. The titers is the highest dilution at which more than half of the organisms exhibited the yellow-green fluorescence around the entire periphery.

A positive titer is considered a reaction at a dilution of 1:16 or greater. Titers of 1:16 to 1:64 visually reflect only some past exposure, perhaps even years previously, but it could also mean early stages of disease if you find a rising titer. Titers of 1:256 may indicate immunity, relatively recent exposure or present involvement. A titer of 1:1,024 is very significant and toxoplasmosis should be considered. In order to make a diagnosis of acute toxoplasmosis you need IFA-IgM test or evidence of a fourfold increase

TABLE II
Comparison of Percent Positive Toxoplasma Antibody Titers by
Age Group in Chronic Renal Patients and a Matched Control

Age Group	Comparative Seropositivity by Age Group			
	Chronic Renal		Control	
	Number	Percent	Number	Percent
10-20	0	0	3	33
21-30	2	33	5	50
31-40	4	57	7	70
41-50	18	62	7	70
51-60	19	58	9	90
>60	9	64	0	0
TOTALS	52	58	31	63

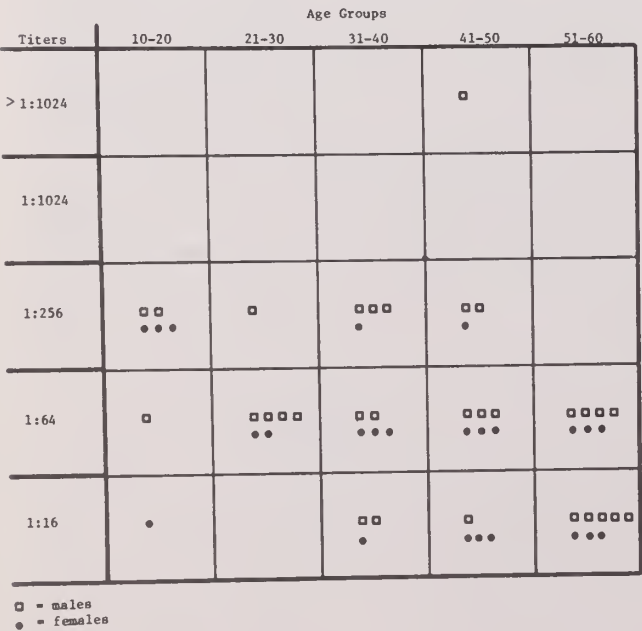


Figure 1: Serologic Titers Distribution by Age and Sex.

in a serologic titer (13, 14).

Results

The distribution of positive toxoplasma antibody titers by age and sex is shown in Table I. By age twenty, thirty-three percent of males and forty percent of females have positive titers, indicating exposure to toxoplasmosis. The percent of persons with positive titers increases with age. The percent rise by age group is faster in the males. Over all sixty-three percent of males and fifty-two percent of females have positive antibody titers for toxoplasmosis.

The distribution of antitoxoplasma titers by age group, sex and serologic titers are depicted in Figure 1. Forty-three out of fifty-seven subjects had titers of less than 1:256. Thirteen out of fifty-seven had titers of 1:256 while only one had a titer of greater than 1:256. There was no difference by age group or distribution of titers.

The percent of positive toxoplasma antibo-

TABLE III
Serologic Titers of Chronic Renal Patients Compared to a Control Group of Patients

Titer	Chronic Renal		Control	
	Number	Percent	Number	Percent
1:16	3/52	5.0	8/31	26
1:64	18/52	35.0	14/31	45
1:256	17/52	33.0	8/31	26
>1:1024	14/52	27.0	1/31	3

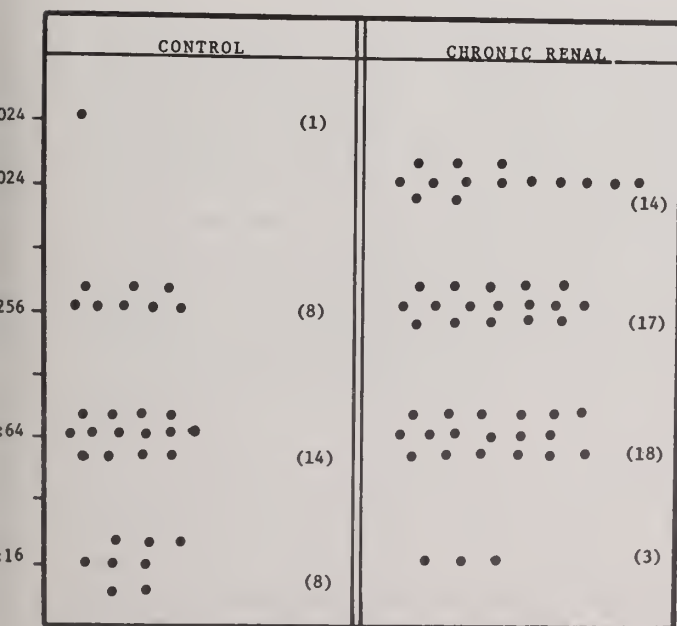


Figure 2: Distribution of toxoplasma antibody titers.

dy titers in chronic renal patients is compared by age groups to a control is prescribed in Table II. By age group the percent of positive serologic titers is lower in the chronic renal group. We were unable to match the group of chronic renal patients over age sixty with a control, but sixty-four percent of these patients

had positive titers. The overall percentage of positive titers is slightly lower in the chronic renal patients (fifty-four vs. sixty-three percent).

The serologic titers of chronic renal patients are compared to a control group of patients in Table III. The percentage of chronic renal patients with positive toxoplasma titers of 1:64 or less was forty percent, in the control it was seventy-one percent. The chronic renal patients tended to have a lower percentage of low titers. Chronic renal patients with positive toxoplasma titers had titers of 1:256 or greater in sixty percent of them, while only twenty-nine percent of the control group had such titers. The above results are depicted graphically in Figure 2. The number of patients represented individually by dots is correlated with the toxoplasma titer.

Discussion

Toxoplasmosis is world wide in distribution, but geographic variation exists in prevalence of positive titers. The prevalence of toxoplasmosis in normal adults in the United States is around 20 percent and varies depending on age and area of the country (8). Epidemiologic surveys reveal generally less infection in humans in cold regions, arid areas and at high elevations. Prevalence is low (10-20 percent)

in Iceland, Northern Sweden and Arizona. In the United States the prevalence is lower in the Mountain and Pacific regions, 3 and 8 percent respectively (8). In many tropical regions the prevalence is 70 percent or higher, like in Tahiti, El Salvador and others (5, 9, 10),

The diagnosis of infection may be established by the isolation of *T. gondii*, demonstration of the protozoa in tissue sections, smears or body fluids, by histologic finding or by serologic tests. The serologic tests are the primary method of diagnosis for most physicians (12, 13). The most frequently used test because of its availability is the indirect fluorescent antibody test (IFAT), which correlates directly with the more time consuming, Sabin-Feldman Dye-Test. These antibodies appear within 1-2 weeks after acute infection, reach high titers (1:1000) in 6-8 weeks and then gradually decline over months to years, low titers (1:4 to 1:64) commonly persist for life and may fluctuate over a limited range. The level of the antibody titer cannot be correlated with the severity of the illness (13).

In 1972 a serologic survey performed in Puerto Rican children and their mothers, showed a prevalence of 8 percent in children age 24 months or younger and 51 percent in their mothers age unspecified (11). While titers were unspecified 10/57 women of childbearing age were reported to have titers of 1:1024, this may have represented recent infections. In our study 63 percent of males and 52 percent females had positive serologic titers, only 4 of 11 females age 40 or less had titers of 1:256 and none had titers greater than the above. Age 40 was taken arbitrarily as a cut off point to select a group compatible with childbearing capacity. Probably none of our females had active infection and the titer of 1:256 represented exposure in the past to toxoplasmosis. In our male population the percent positives increased with age as occurred in the females. The equal prevalence by sexes has been described in almost all of the serologic survey (5).

In Puerto Rico a significant proportion of our population is positive for toxoplasmosis but most of the individuals carry low titers indicating exposure and no active disease. In order to diagnose acute toxoplasmosis you need a rising serologic titer of a fourfold increase over at least a two-week period

and preferably indication of a positive fluorescent antibody titer to IgM (12, 13). The transmission of toxoplasmosis from mother to fetus usually occurs during an episode of acute toxoplasmosis in the mother. If a woman with a positive stable titer becomes pregnant, the risk of transmission to the fetus is probably nil. Many women with positive titers deliver a normal conceptus and the relation to abortions is undefined. The documentation of a high serologic titer 1:1024 or greater in a woman is indicative of active infection and she should be treated; if pregnant, consideration to a therapeutic abortion should be given. There is no evidence of direct human to human transmission other than mother to fetus, therefore, the mother or father will not transmit the disease to other members of the family.

After multiplication at the site of entry the trophozoites disseminate via the blood and lymphatics and may invade all organs and tissues. The development of humoral and cellular immunity resolves the acute infection and many of the parasites are destroyed, although those organisms which have formed tissue cysts survive. While both humoral and cell mediated immunity are important, the last appears to play a major role in host defense (14). In immunodeficient hosts the acute infection may persist to cause severe necrotizing lesions. In immunocompetent hosts when infected, the acute infection resolves, the trophozoites disappear and tissue cysts form. Tissue cysts formation appear to be enhanced by the appearance of specific antibody, these cysts retain the potential for reactivation (15).

In our chronic renal patients we found that the overall percent of positive titers was lower than the control group, at every age group studied. This may be a reflection of lower exposure or a defect in production of antibodies in these patients. Most significant is that while the percent of positives was lower, the percentage or number of patients with high titers was two times higher in the chronic renal group than in the control (60 vs. 30 percent). This is probably a reflection of a defect in cell mediated immunity in which the cyst is able to reactivate and the development of antibodies increases. It is likely that clinically apparent and actively serologically toxoplasmosis is most often a consequence of reactivation of latent infection (16). The chronic renal pa-

tient should be followed serially with toxoplasma antibody titers. If these patients have positive titers these should be repeated at every febrile episode. If there is a fourfold rise in titer or a single isolated titer of 1:1024 or greater they should be treated.

Acknowledgements

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DIPHTHERIA: SEROLOGIC STUDY OF 422 PERSONS IN PUERTO RICO

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Summary: Diphtheria is a rare cause of morbidity in Puerto Rico and is a preventable disease, utilizing immunization with diphtheria toxoid. A study was designed to determine the percent of persons by age group that had protective diphtheria antitoxin titers defined as 0.01AU/ml or greater. The overall percent of subjects with protective titers was 85.5 percent and similar for both males and females (83.9 percent and 88.1 percent). When looked by age groups, 95 percent of the persons less than 21 years of age had protection. The percent of persons with protective titers decrease with age to a low of 71.4 percent of the persons in the 81-90 age group. While in most temperate climates the percent of persons with protection is similar to the present report, the levels of protective titers in our study are higher, this is probably a reflection of subclinical infection with *Corynebacterium diphtheria* in our population, including skin and pharyngeal colonization. The present immunization practices against diphtheria in Puerto Rico need not to be changed, but emphasis on the use of tetanus diphtheria toxoids adult type (Td) in the elderly population should be given.

Introduction

There has been widespread immunization of persons with diphtheria and tetanus toxoids. In

the United States the occurrence of diphtheria has fallen following immunization campaigns, from an incidence of 55 cases per 100,000 population in 1930 to 0.14 cases per 100,000 population in 1975 (1). In general immunized patients have a milder illness than unimmunized ones. Full immunization with diphtheria toxoid does not prevent nasopharyngeal carriage of the organism but significantly reduces the case fatality ratio, and also ameliorates the symptoms of active disease. Most cases of diphtheria occur in unimmunized individuals, the overall death rate in the United States is around 10 percent. Diphtheria is a preventable disease, immunization being effective and involving little risk of sequelae.

In Puerto Rico the data for diphtheria is not easily retrievable. There was a massive island-wide immunization effort during 1966-67, when the Health Department administered 511,645 doses of DPT to children under five years of age and younger; 1,628,933 doses of Td to persons between the ages of five and 19; and 1,255,191 doses of Td to persons age 20 and older (2). After the 1966-67 campaign the Health Department continued to provide the vaccine free, but no mass campaign was carried out. Previous studies in the United States have revealed progressive decline in antibody titers to diphtheria with age (3, 4, 5). This study was designed to determine present level of immunity in a group of 422 Puerto Rican subjects and to identify by age groups possible susceptible the percent of subjects with and without protective titers.

Material and Methods

A group of 422 subjects were requested to parti-

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cipate in the study. All subjects were interviewed by one of the authors and a questionnaire filled. The subjects studied consisted of 254 males and 168 females. The age range of the males was from 17 to 90 and the age range for females was from 13 to 77. Most of the subjects lived in urban areas, and represented various socioeconomic groups.

All subjects were bled after the interview and the serum separated and divided into small aliquots. The serums were stored frozen in a Revco ULT-1285 freezer (West Colombia, S. C.) at -70°C , and kept at that temperature until they were thawed for antitoxin determinations. Aliquots of serum specimens obtained from the patients were used to detect diphtheria antitoxin levels using the indirect hemagglutination assay of Stavisky (5) and modified by the Center for Disease Control. Diphtheria antitoxin protection was defined as 0.01 antitoxin units per ml or more (3).

Preparation of sheep cell suspension and tanning of cells.

Sheep red blood cells in Alsever's solution were washed three times in phosphate buffered saline, PBS, pH 7.2 (110 ml 0.3M NaCl, 23.9 ml 0.15 KH_2PO_4 and 76.0 ml 0.15M Na_2HPO_4) and then packed by centrifuging for ten minutes at 1,700rpm. A 2.5 percent suspension was made with 39 volumes of PBS pH 7.2 to 1 volume of packed cells. These cells were tanned at 37°C for 20 minutes with an equal volume of freshly prepared 1:20,00 (w/v) tannic acid (Mallinckrodt, St. Louis, Mo.) in pH 7.2 PBS.

Sensitization of sheep erythrocytes.

The tanned cells were washed twice with pH 5.0 PBS (100 ml 0.3M NaCl and 100 ml 0.15M KH_2PO_4) and resuspended to 2.5 percent in pH 5.0 PBS and divided into two portions. One portion was mixed with an equal volume of diphtheria toxoid (2,700 Lf/ml) diluted 1:4 in pH 5.0 PBS and second portion with an equal volume of pH 5.0 PBS without toxoid. This concentration of toxoid for sensitization of sheep erythrocytes was determined to be optimal in preliminary titrations. Sensitization was carried out at room temperature for 15 minutes with agitation on a reciprocal shaker. Diphtheria toxoid was supplied by Staten Serum Institute, Copenhagen, Denmark. After sensitization the cells were washed three times in pH 7.2 PBS containing 1 percent normal rabbit serum, 0.006 percent Methiolate and 0.0042 percent sodium borate and were suspended at 0.4 percent in this diluent. The sensitized sheep erythrocytes remained stable for 7 to 10 days at 4°C , but after this time began to agglutinate spontaneously. Sheep erythrocytes used to absorb sera were collected in Alsever's solution, washed three

times in pH 7.2 PBS, and suspended in the above 1 percent normal rabbit serum diluent to a hematocrit of 33 percent.

Hemagglutination assays.

Samples of 0.2 ml of all serum specimens were mixed with 0.3 ml aliquots of 33 percent sheep erythrocytes and adsorbed for 15 minutes at room temperature. The adsorption mixtures were centrifuged at 1,200g for five minutes and the supernatants were used for titration of antitoxin. Normal rabbit serum diluent, 0.05 ml, was added to all cells except for the first column in microtiter plates. Adsorbed serum specimens, 0.10 ml, were placed in the first column. Two-fold serial dilutions were performed by successive transfers of 0.05 ml volumes with a microtiter diluter. Samples of 0.4 percent sensitized or control erythrocytes, 0.05 ml, were added to appropriate rows. Assays for diphtheria antitoxin and control for non-specific hemagglutination were performed at the same time. Antitoxin used was U. S. Standard diphtheria antitoxin, Lot No. A36, 5 units per ml obtained from the Division of Biologics Standard, National Institutes of Health, Bethesda, Maryland. This was diluted to 0.1 u/ml and were included as standards in each experiment. After 18 to 24 hours of incubation at room temperature the plates were examined. In each assay the dilution immediately preceding the first cell with a discrete button of erythrocytes, was accepted as the end point. The number of antitoxin units per ml of each serum specimen was calculated by comparison with the standard antitoxins.

Results

The distribution by sex and age groups of the 422 studied subjects and the number and percentage of protection by age group is presented in Table I. For population studies, antitoxin titers are usually determined by hemagglutination and studies have demonstrated a good correlation between antitoxin titers measured by hemagglutination and neutralization techniques (7).

The overall protection of the 422 subjects was 85.5 percent. The protection by age group decreased from 94 percent in persons aged 30 years of age or less to 71 percent in the group 81 to 90 years old. In spite of this decrease in percent of subjects protected, those protected had antitoxin titers above the minimal protective level. The percent of subjects

TABLE I

Distribution by age groups and sex, of the number and percent of subjects with protective diphtheria antitoxin concentrations, defined as 0.01 AU/ml or greater

Age (Years)	Total number of subjects	Subjects with protective concentrations	
		Number	Percent
<21	38	36	(94.7)
21-30	155	147	(94.8)
31-30	47	41	(87.2)
41-50	51	41	(80.4)
51-60	85	62	(72.9)
61-70	25	18	(72)
71-80	14	11	(78.6)
81-90	7	5	(71.4)
Sex			
Females	168	148	(88.1)
Males	254	213	(83.9)
TOTAL	422	365	(85.5)

with protective antitoxin titers were similar for males and females.

In Figure 1 the distribution of diphtheria antitoxin titers in the studied subjects is shown. There is a bell shaped distribution with 175 subjects having diphtheria antitoxin titers from 0.08 to 0.32 antitoxin units per ml and 61 subjects having titers of less than 0.01 AU/ml, therefore lacking protection. The rest of the subjects have either intermediate titers or titers greater than 0.64 AU/ml.

In Figure 2 the distribution of geometric mean titers of diphtheria antitoxin by age is shown. As age increases the geometric mean titer decreases; in spite of this decrease most subjects studied have

protective levels. The very high titers in earlier years may be a reflection of immunization practices and exposure to groups with high rates of nasopharyngeal diphtheria carriage. As the age increases there is less exposure to better vaccines and younger age groups reflected by a declining titer, but still same subclinical pharyngeal infection to maintain immunity.

Discussion

It is of interest that the majority of subjects

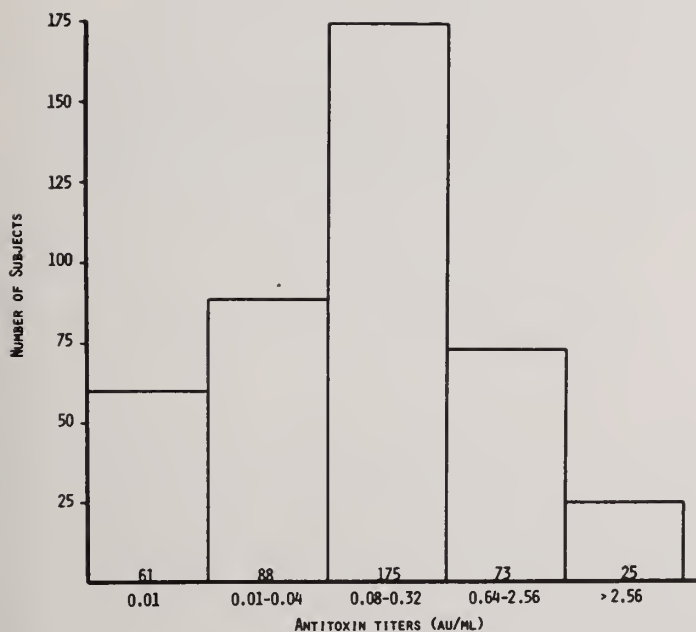


Figure 1: Distribution of titers of diphtheria antitoxins.

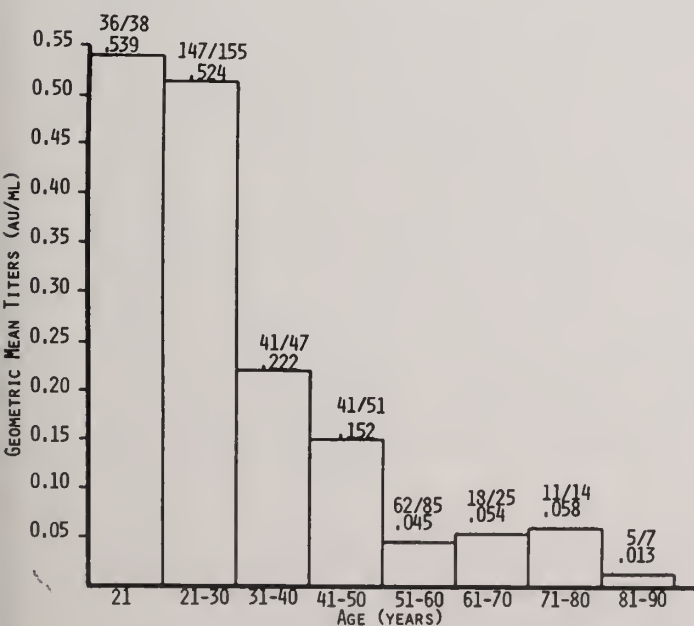


Figure 2: Distribution of geometric mean titers of diphtheria antitoxins by age. The numbers above the bars are the geometric mean titers for each age group. Above those numbers are the fractions of individuals in each group whose antitoxins titers are greater than 0.01 Au/ml. Data presented is from 422 subjects.

(85 percent) included in this survey have protective titers against diphtheria and therefore are probably adequately immunized. The titer of diphtheria antitoxin required to prevent or modify this disease is unknown. Most studies of diphtheria immunity have defined protection as 0.01 units/ml, we utilized this level for the present study (3, 5).

The findings about diphtheria immunity in the present study do not substantially differ from the results of previous investigations when we look at overall protection. More than a decade ago, Levine and Loyman, (5) noted that most subjects older than 30 years of age did not have diphtheria antitoxin levels greater than 0.01 unit/ml. In the present study when we look at protective levels in Puerto Rico the titers are much higher, than in studies in temperate climates. A recent British investigation reported that 47 percent of residents in an elderly persons home had diphtheria antitoxin titers below 0.01 unit/ml (8). In Puerto Rico, like in most tropical climates, there is probably a higher incidence of subclinical diphtheria, which may account for the observation that most adults have higher protective levels of diphtheria antitoxin when compared to studies in the temperate zones. Another possible explanation is the use of diphtheria toxoid together with tetanus toxoid (Td) when the latter is administered, but this is not a routine practice in Puerto Rico. Subclinical infection with *Corynebacterium diphtheriae* of either skin or pharynx seems the most likely possibility.

Diphtheria immunization in Puerto Rico should continue as it is practiced today, but we should look specifically into the elderly living in nursing homes to assure protection. In this specific group of people and in people in our island age 50 or older which require tetanus immunization the use of tetanus diphtheria toxoid of adult type (Td) is desirable. After a primary immunization a booster every 10 years would assure continued protection for all.

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ABNORMAL HEMOGLOBINS DETECTED IN SCREENING OF PUERTO RICAN POPULATION

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Abstract: Five thousand four hundred seventy three individuals, (5,473) including newborns, adolescents, pregnant women and adult males from San Juan, Puerto Rico and nearby towns were tested for abnormal hemoglobins in 1977-78. Two hundred ten (210) cases of abnormal hemoglobins (3.90 percent) were encountered, including 190 (3.5 percent) of HbS and 20 (0.4 percent) of HbC, excluding possible cases of thalassemia trait. Among adolescents from the San Juan Area the prevalence of HbS and C was 4.2 percent. But the prevalence among 751 adolescents from the town of Loíza was 8.7 percent.

Analysis of the data indicates that we are dealing with two different populations: one from the town of Loíza (20,000 population) with a prevalence of 8.7 percent; and that of the general population of San Juan and nearby towns (about 1,000,000 people), with a prevalence of 3.1 percent. The finding of 210 cases of abnormal hemoglobins, including two (2) of HbSS, among 5,473 screenees, and 177 of HbAS among 512 referred cases indicate that there is a need for a continued effort to provide education, screening and genetic counseling to the Puerto Rican population.

Abstracto: Cinco mil cuatrocientos setenta y tres personas, incluyendo neonatos, adolescentes, muje-

res embarazadas y varones adultos de San Juan y pueblos cercanos fueron examinados para detectar hemoglobinopatías por electroforesis en 1977-78. Se encontraron 210 casos (3.90 por ciento) de hemoglobinas anormales, incluyendo 190 (3.5 por ciento) de Hb S y 20 (0.4 por ciento) de Hb C. La prevalencia de Hb S y C entre los adolescentes del área de San Juan fue de 4.2 por ciento. Pero la prevalencia en adolescentes del pueblo de Loíza fue de 8.7 por ciento.

Los datos indican que la prevalencia de Hb AS y AC en la población cercana, excluyendo a Loíza, es de 3.1 por ciento, la cual es claramente distinta a la prevalencia en la comunidad de Loíza (8.7 por ciento). El hallazgo de 210 casos de hemoglobinas anormales incluyendo dos de Hb SS entre 5,473 personas cernidas y 177 de Hb AS entre 512 personas referidas indican que hay una necesidad para continuar proveyendo educación, detección y consejería sobre hemoglobinopatías en la población puertorriqueña.

Sickle cell disease is one of the most important hereditary diseases in many countries (1). The sickle cell gene reaches a high prevalence in some ethnic and geographic areas of the world. The highest gene concentration occurs in equatorial Africa, where up to 40 percent of West African people possess the hemoglobin (HbS) gene. It is also relatively common in those regions in America directly linked to the slave trade of the seventeenth and eighteenth centuries, namely United States of America, Brazil, Caribbean and Central American countries. The gene is also present in Southern Italy, Sicily, Central Regions of Greece, India and the Middle East (1).

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The prevalence of the sickle cell gene in the North American black population has ranged between 6.0 per cent and 12.0 percent (2). The incidence of sickle cell disease in newborns has ranged from 0.1 percent to 0.5 percent (3).

The prevalence of the sickle cell gene in Puerto Rico has been reported in the past to range between 2.3 percent and 6.5 percent (4, 5, 6 and 7).

Population samples studied and reported consisted of persons or patients as they came to testing centers. Furthermore, in some instances the laboratory techniques used did not differentiate hemoglobin S from other abnormal hemoglobins which might have a similar electrophoretic pattern. Therefore, valid conclusions cannot be drawn from these studies regarding the real prevalence of hemoglobin S in our community.

In August 1977 the Bureau of Child Health Services of the U. S. Department of Health, Education and Welfare made a contract with the Department of Health of Puerto Rico to conduct a Sickle Cell Anemia Screening and Education Clinic in this Island.

The clinic was established in the University Children's Hospital, Puerto Rico Medical Center in Río Piedras, Puerto Rico.

The findings of the screening and confirmatory testing for abnormal hemoglobins in the population studied in 1977-78 are the subject of this report.

Material and Methods

Screening and education services were directed to those groups which were expected to benefit more from the program. The groups studied, totaling 5,473 individuals, included newborns, adolescents and adults in the reproductive age. The group of newborns consisted of 1,530 term babies taken at random from the San Juan Municipal Hospital and the University Children's Hospital.

The adolescent group consisted of 2,043 school children. Approximately half of them lived in the San Juan metropolitan area, and the rest came from the towns of Loíza and Río Grande which are about 15 and 25 miles east of San Juan, respectively. Schools and student groups were chosen by an accepted statistical randomized method with

proportional representation of public and private schools.

The group of adults in the reproductive age was composed of 1900 individuals, including 1,047 women from prenatal clinics, 762 men from the Puerto Rico National Guard, and 91 Medical Students. The latter group was made up of individuals taken as they showed up in the testing clinic.

In newborns, blood was obtained from the heel in heparinized capillary tubes. Blood samples in adolescents and adults were taken by venipuncture in EDTA tubes. Informed consent was obtained before including the individuals in the study.

Information on abnormal hemoglobins, and specially on sickle cell hemoglobin, was provided to most persons. Confidentiality was maintained by means of the use of a code number in each case.

Hemoglobins were identified by electrophoresis utilizing Helena Electrophoresis Units* with cellulose acetate membranes at pH 8.4-8.6, according to C. D. C. specifications (8). All cases beyond newborn age showing hemoglobin in a position corresponding to the pattern SDG were checked for presence of hemoglobin S by the solubility test (9). All newborns with an electrophoretic pattern showing or suggesting Hb SDG or CEO on cellulose acetate, as well as individuals beyond newborn age showing the CEO pattern, were rechecked by the citrate agar electrophoresis method, at pH 6.0-6.2 (10). Final confirmation of Hb AS versus Hb SS in newborns was performed by retesting of infants at ages 4 to 6 months.

Results

Five thousand four hundred seventy three (5,473) individuals were tested in screening clinics. They showed 212 abnormal hemoglobins including 190 cases of Hb S and 20 of Hb C, for an overall prevalence of 3.9 percent.

Forty six out of 1,530 newborns (3.0 percent) showed abnormal hemoglobins including 39 Hb S and 7 Hb C. (See Table I).

Twenty seven (27) positive cases were encountered among 1,047 pregnant women tested (2.6 percent). That number included 25 cases of Hb S and 2 of Hb C. The prevalence of Hb S and C among 762 adults tested in the National Guard Camp was

* Helena Laboratories, Beaumont, Texas.

TABLE I
 Findings in Various Groups Tested for HB S and HB C

Group	Number Cases	Abnormal Hemoglobins	Percent
Newborns	1,530	46	3.0
Women Prenatal Clinics	1,047	27	2.6
National Guardsmen	762	17	2.2
Medical Students	91	0	0
Adolescents	2,043	122	6.0
TOTALS -	5,473	212	3.9

TABLE II
 Findings in Adolescents Tested for Abnormal Hemoglobins

Group	Number Cases	Abnormal Hemoglobins	Percent
Loíza	751	65	8.7
Río Grande	203	11	5.4
San Juan	1,089	46	4.2
TOTAL S-	2,043	122	6.0

2.2 percent.

Two thousand forty three (2,043) adolescents were tested and 122 (6.0 percent) had an abnormal hemoglobin, including 113 Hb S and 9 Hb C. However, as shown in Table II, the prevalence of ab-

normal hemoglobins varied significantly among the groups from the three towns studied: in San Juan 4.2 percent, in Río Grande 5.4 percent, and in Loíza (8.7 percent). The difference among these groups is statistically significant.

Among 5,473 individuals screened there were 2 cases of Hb SS and 188 of Hb AS for an over all Hb S prevalence of 3.5 percent. Twenty cases of Hb AC were encountered, for a Hb C prevalence of 0.4 percent.

Five hundred twelve (512) persons were referred for confirmatory testing and/or to rule out a hemoglobinopathy. Two hundred seventeen (217) were found to have abnormal hemoglobin (42.4 percent). Twenty nine (29) patients with Hb SS and eleven with other serious hemoglobinopathies have been encountered among these referred cases.

Discussion

The survey conducted during 1977-78 in the Puerto Rico Sickle Cell Anemia Clinic indicated that the overall prevalence of abnormal hemoglobins in the whole group studied was 3.9 percent, if possible cases of thalassemia trait are excluded. As expected, the most common abnormal hemoglobin found was Hb AS, with a general prevalence of 3.54 percent. The finding of 20 cases of Hb AC, for a prevalence of 0.4 percent was also significant.

When we analyzed the data obtained in the various groups studied, we could identify two different populations: one from Loíza and the other from the general San Juan population.

Loíza is a small town in the north coast, 15 miles East of San Juan, which has a population of about 20,000 people with a high percentage of black people. This population, represented by 751 adolescents taken at random in the Loíza intermediate and high schools, showed a Hb AS and Hb AC prevalence of 8.7 percent. This figure, which is similar to what has been reported in the black population of U. S. A., is statistically different from the value for the rest of the group studied.

The sample of 4,673 individuals taken outside of Loíza, composed of women from the Puerto Rico Medical Center prenatal clinic, newborns attended in the University and San Juan City Hospitals, school children from San Juan and Río Grande, medical students and National Guardsmen, showed a Hb S prevalence of 3.1 percent.

Data on the site of birth of the individuals,

and point of origin of their parents, indicate that many Puerto Rican towns are reasonably well represented in this large sample. Data available in our laboratory suggest that the prevalence of Hb S in the island's central towns is below the figure found in San Juan. Therefore, we believe that this value (3.1 percent) is higher than the mean for the whole island. Additional studies are in progress to confirm this hypothesis.

In the survey of school children in San Juan, we encountered a group of students which seemed to have a higher prevalence of Hb S. No socioeconomic differences, nor evidence of displacement of population from Loíza to that area was apparent. Examination of the site of origin of these children's parents showed that a large proportion of them came from the Dominican Republic. Further investigation has confirmed that there is a high prevalence of Hb S in that country, and that a large number of Dominicans has settled in the neighborhood where this particular school is located (11).

Several studies conducted in Puerto Rico during the last four decades have reported figures for prevalence of Hb S ranging from 2.0 percent to 4.2 percent in the general population (4-7). Our study of a larger and statistically more significant sample has shown a prevalence of 8.7 percent in Loíza, and 3.1 percent in the rest of the group surveyed. This means that hemoglobin S is as frequent in Loíza as in black populations in U. S. A. and in some Caribbean Countries (2, 3, 12). But the prevalence in San Juan and in nearby towns, except Loíza, is about one third as high.

The expected incidence of sickle cell anemia (Hb SS) in newborns, on the basis of the known pattern of inheritance of Hb S, must be 1 per 500 births in Loíza, and 1 per each 3,500 births in the rest of the population studied. This projected incidence is sufficiently high to result in a large number of patients with sickle cell anemia in a population with a birth rate of 22 per 1,000 persons and 75,000 live births annually.

The findings in our screening program during 1977-78 indicate that there is a need for a continued effort to provide screening and education on sickle cell disease, and genetic counseling to persons who are carriers of sickle cell hemoglobin.

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HEPATITIS VIRAL: ESTUDIO SEROLOGICO EN PUERTO RICO, REVISION Y REPASO DE LA LITERATURA - 1981

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Introducción

La hepatitis viral es una enfermedad de distribución mundial de la cual ya se hace mención desde el tiempo de Hipócrates (1, 9, 77). En los Estados Unidos se reportan anualmente entre 50 y 60 mil casos subclínicos y los no reportados hacen que la cifra estimada sea de unos 300,000 (2, 7). La mortalidad registrada en los Estados Unidos es de unos 3,000 casos por año (1 por ciento) de los cuales casi en su totalidad se deben al virus de la hepatitis B y al de la hepatitis no-A, no-B (3). Los problemas que origina la hepatitis viral no solo afectan al paciente que acude a nuestros hospitales con los clásicos síntomas de lasitud, disturbios gastrointestinales e ictericia, sino que constituye también un serio problema para los demás pacientes, los cuales por las circunstancias que veremos más adelante se ven expuestos a esta enfermedad. También el personal que atiende a estos pacientes está expuesto y en la actualidad la hepatitis viral es la enfermedad ocupacional que más afecta al personal de nuestros hospitales (4).

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En el siguiente trabajo presentaremos algunos datos epidemiológicos relacionados con la hepatitis viral, los cuales fueron obtenidos en el Hospital de Veteranos de San Juan, Puerto Rico.

Diseño del Estudio

Durante los meses de diciembre de 1979 a febrero de 1980 se obtuvieron muestras de sangre de pacientes y personal del Hospital de Veteranos de San Juan, Puerto Rico. Las áreas incluídas en el estudio fueron las siguientes: hemodiálisis (pacientes y personal), laboratorio clínico (personal), dental (personal) y donantes voluntarios. Se obtuvieron 199 muestras de sangre que se procesaron para antígeno australiano (HBsAg), anticuerpos contra antígeno australiano (anti-HBs) y anticuerpos contra el virus de la hepatitis A (Anti-HA) usando la técnica de radioinmunoensayo descrita anteriormente (5, 6).

Resultados

Un total de 199 personas se incluyeron en el estudio: 70 de la Sección de Hemodiálisis (52 pacientes y 18 miembros del personal). Veintiuno de la Sección de Odontología, 30 de la Sección del Laboratorio Clínico y 78 del grupo de donantes voluntarios.

En la Tabla I veremos la distribución de los

TABLA I

**Incidencia de HBsAg, anti-HBs y anti-HA en diversas áreas del
Hospital de Veteranos de San Juan, Puerto Rico
(diciembre 1979 - enero 1980)**

Sección	No.Total	Edad	HBsAg	anti-HBs	anti-HA
Pacientes hemodiálisis	52	25-85 (70.9)	2 (3.8 por ciento)	16 (30.7 por ciento)	50 (96.1 por ciento)
Personal hemodiálisis	18	25-56 (38.4)	0	3 (16.6 por ciento)	15 (83.3 por ciento)
Dental	21	25-63 (40.6)	1 (4.7 por ciento)	2 (9.5 por ciento)	13 (61 por ciento)
Laboratorio Clínico	30	23-60 (36.8)	0	5 (16.6 por ciento)	19 (63.3 por ciento)
Donantes	78	18-60 (28.2)	0	13 (17 por ciento)	52 (67 por ciento)

casos de acuerdo con la positividad para las diferentes pruebas realizadas. Solo tres personas resultaron positivas para HBsAg, dos pacientes de hemodiálisis y un empleado de odontología. Esto representa un 1 por ciento del total de las muestras obtenidas. Treintinueve resultaron positivas para anti-HBs para un 19 por ciento del total. Ciento cuarentinueve fueron positivas para anti-HA para un 74 por ciento del total.

Al analizar los datos y comparar los distintos grupos vemos que 4 por ciento eran positivos para HBsAg en el grupo de hemodiálisis y el de odontología. Los demás grupos no mostraron positividad para ese antígeno. Hubo similitud entre los distintos grupos en cuanto a anti-HBs: donantes 17 por ciento, laboratorio clínico 16 por ciento, odontología, 9.5 por ciento y el personal de hemodiálisis 16 por ciento. Sin embargo, el grupo de los pacientes de hemodiálisis con un 30 por ciento de positividad, duplicó al grupo del laboratorio y de dental. Todos los grupos mostraban altos porcentajes (mayor de 50 por ciento) en el resultado de anti-HA siendo los del grupo de pacientes y del personal de hemodiálisis

los más altos con 96 por ciento y 83 por ciento respectivamente.

Discusión

Hepatitis A (Hepatitis infecciosa)

El número de casos de HA reportados al CDC (Centro de Control de Enfermedades) en Estados Unidos para 1978 fue de 29,500 (7). Es probable que esta incidencia sea mucho mayor, ya que muchos casos cursan de forma subclínica y no son diagnosticados (8). Otros muchos no son reportados (2, 9).

La hepatitis A se transmite a través de la ruta oro-fecal y su período de incubación es de dos a seis semanas (10). Usualmente se presenta en brotes y con frecuencia en instituciones tales como: escuelas, guarderías infantiles, asilos de envejecientes, campamentos militares y prisiones (11-13). Es común el ver a varios miembros de una familia sufrir la enfermedad. Los niños menores de dos años (edad

TABLA II

Curso de la Infección por el Virus de Hepatitis A

1. Período de incubación	20 a 45 días (promedio de 28 días)
2. Partículas del antígeno	se detecta varios días antes de la elevación de las transaminasas y finaliza con el pico de las mismas.
3. Anticuerpo IgA contra el virus de HA	surge durante la fase clínica, alcanza su pico entre las semanas 10-16 y permanece presente por muchos años incluso de por vida.
4. Anticuerpo IgM contra el virus de HA	surge durante la fase clínica y puede persistir por varias semanas

del pañal), adquieren con relativa facilidad la hepatitis A en guarderías infantiles (14). Estos niños suelen evolucionar de forma subclínica, pero transmiten la enfermedad a sus padres o sus hermanos mayores quienes usualmente la sufren de forma aparente.

Los vehículos más frecuentemente implicados en la transmisión de la hepatitis A son el agua, la leche, ostras y los mariscos (12, 15, 16). Un estudio epidemiológico reciente señala que la variación en la incidencia de hepatitis A atribuible a las características del agua es probablemente menor del 8 por ciento de los casos de la hepatitis A reportados en los Estados Unidos anualmente (17).

Clásicamente la hepatitis A se ha considerado una enfermedad benigna con morbilidad y mortalidad bajas (18). Existen casos reportados de hepatitis A fulminante confirmados por estudios de anticuerpos (19). Recientemente fue publicado un caso confirmado por inmunofluorescencia directa de tejido hepático (20). Se piensa que la patogénesis de la hepatitis B fulminante se relaciona con una respuesta hiperinmune; sin embargo, la patogénesis de la hepatitis A fulminante, de acuerdo a los hallazgos del caso anterior, parece residir en el grado má-

ximo de afectación celular y no en la respuesta inmune que se encontró normal.

Los estudios hechos revelan que la excreción del virus se mantiene desde tres semanas antes hasta ocho días después del comienzo de la ictericia y la mayoría de los autores concuerdan en que la infectividad finaliza con el pico de las transaminasas (21, 22). Cuando surgen los síntomas, dos terceras partes de los pacientes han dejado de eliminar el virus en la excreta (1). El incremento de anticuerpos IgG anti-HA contra el virus de la hepatitis A es lento y una vez aparecen pueden permanecer de por vida. Por esto no son de mucha utilidad en el diagnóstico de hepatitis aguda. Los anticuerpos IgM anti-HA son específicos, surgen en la fase aguda y pueden persistir durante un promedio de 84 días después del comienzo de la enfermedad lo que les hace ser el marcador ideal para el diagnóstico de hepatitis aguda tipo A (23). Desafortunadamente no muchos centros cuentan con estas facilidades y hoy por hoy en la mayoría de los hospitales el diagnóstico de hepatitis A se hace a expensas de la clínica y los datos epidemiológicos.

Edad y Nivel Socioeconómico

TABLA III

Curso de la Infección por el Virus de Hepatitis B

1. Período de incubación	4-28 semanas (60-110 días)
2. Antígeno australiano o HbSAg	se detecta entre la sexta y doceava semana después de la exposición y persiste por una a seis semanas.
3. Partícula de Dane o DNA	surge poco después del HbSAg, alcanza el pico al final del período de incubación y desaparece al comienzo de la fase clínica.
4. Antígeno e o HBeAg	aparece al final del período de incubación y desaparece antes de finalizar la fase clínica.
5. Anticuerpo contra core o anti-HBc	se detecta poco antes del comienzo de los síntomas, logra su pico semanas después de la fase clínica y declina durante el primer año desapareciendo al cabo de 5-10 años.
6. Anticuerpo contra antígenos o anti-HBs	se detecta meses después de desaparecido de la sangre el HbSAg; permanece por años y se asocia con protección.
7. Anticuerpo contra el antígeno e o Anti-HBe	se sabe poco al respecto, algunos estudios señalan que se puede detectar semanas después de desaparecido el HBeAg y su duración es de varias semanas.

Un estudio realizado entre los diversos grupos sociales de la ciudad de Nueva York demostró una incidencia de 45 por ciento de anti-HA (24). La incidencia aumentaba con la edad de los individuos y era inversamente proporcional al nivel socioeconómico de los mismos. El individuo viejo estuvo expuesto de forma continua al virus durante toda su vida y por otro lado su niñez fue probablemente más limitada en recursos que la del niño común de hoy. El bajo nivel socioeconómico se relaciona con hacinamiento, malos hábitos y pobre higiene. Todo ello redundo en mayor exposición al virus de la hepatitis A. Estudios similares hechos en Suecia y en Finlandia revelaron una incidencia global de anti-HA de 37 por ciento para cada uno y guardaba la misma relación con edad y nivel socioeconómico que el estudio anterior (25, 26).

No es posible establecer patrones de comparación entre resultados de estudios hechos a nivel de ciudades y los obtenidos en una muestra representativa de una institución hospitalaria, no obstante, esto quizás nos ayude a tener una idea clara sobre el significado de los datos encontrados en nuestro estudio.

En la Tabla I vemos desglosados los distintos grupos analizados, las edades comprendidas y el por ciento de positividad de la prueba de anti-HA. La incidencia total fue de 75 por ciento. Al detallar estos resultados encontramos un 96.1 por ciento entre los pacientes y 83.3 por ciento en el personal de hemodiálisis; un 61 por ciento en el personal de odontología; 67 por ciento en los donantes, y un 63.3 por ciento en el personal del laboratorio clínico.

¿Qué factores son responsables de tan alta

incidencia en nuestro hospital? La edad promedio de 70 años en los pacientes de hemodiálisis podría explicar su alta incidencia. Sin embargo, los donantes cuya edad promedio fue de 28 años mostraron una incidencia mayor que la de odontología y el laboratorio cuyas edades promedio fueron 36 y 40 años respectivamente. Tal vez el nivel socioeconómico pudiera ser un factor determinante en estos resultados. No obstante, nos preguntamos si existen otros factores.

Hábitos

En un estudio hecho por Norkrans se analizaron 107 pacientes de hepatitis A, 297 de hepatitis B y 63 de hepatitis no-A, no-B para un total de 467 pacientes (27). Entre los casos de hepatitis A, 50 pacientes (47 por ciento) eran adictos a drogas; 18 (16.8 por ciento) contactaron áreas endémicas; 24 (22.4 por ciento) negaban exposición obvia y ninguno había recibido transfusiones de sangre. En nuestro estudio no se determinó la población de adictos aunque estimamos que no sería significativo. Sabemos que los adictos a drogas conviven en hacinamiento y pobre higiene (78).

Transfusiones de sangre y hemodiálisis

Varios estudios parecen confirmar el hecho de que la transmisión del virus de la hepatitis A a través de transfusiones de sangre o de pinchazos de aguja resulta poco probable y esto se debe a que la viremia en la hepatitis A es breve y tampoco se ha constatado la existencia de portadores crónicos (8, 10). El virus parece mantenerse en la población de forma subclínica en los períodos interepidémicos. Estudios hechos en pacientes de cirugía recipientes de transfusiones de sangre en el tiempo próximo a la cirugía no demostraron adquisición de esta enfermedad (28-30). Igual resultado hubo en el caso de talasémicos y hemodializados transfundidos múltiples veces y durante años (31-33). Los trabajos de Szmuness permiten concluir que las condiciones epidemiológicas del ambiente de diálisis no contribuye de forma significativa a la diseminación de la hepatitis A (33). En estos estudios se vio que la incidencia de

anti-HA fue equiparable a la de la población control. Tampoco hubo correlación entre duración en el empleo en la unidad o tiempo en hemodiálisis e incidencia de anti-HA.

Alimentos

Gracias al descubrimiento de Feinstone y colaboradores en 1973 el antígeno del virus de la hepatitis A puede hallarse en excreta a través de "microscopía electrónica inmune" (34). Esto ha permitido realizar muchos estudios sobre brotes de hepatitis A en algunos de los cuales se ha podido identificar el foco de infección y el vehículo de transmisión (15, 23). El estudio de Levy en un brote de 107 casos tuvo su origen en un empleado de una cafetería que tenía a su cargo la preparación de emparedados los cuales contaminaba por medio de sus secreciones orofaríngeas (35). Este mismo vehículo fue vinculado a otro brote esta vez a nivel de un hospital de 347 camas, donde se diagnosticaron 44 casos clínicos y 22 subclínicos entre el personal en un período de dos meses (36). El papel que desempeñaron los alimentos y el personal que los manipula no fue objeto de análisis en nuestro estudio, pero cabe mencionarlo como un posible factor contribuyente.

La detección temprana de un foco de hepatitis A permite tomar medidas para interrumpir el brote. Si se detecta el foco de origen este debe separarse hasta tres semanas del comienzo de la ictericia o elevación de enzimas. Los posibles contactos deben identificarse y darle profilaxis con inmunoglobulina sérica durante el período de riesgo.

La inmunoglobulina sérica puede administrarse pre-exposición en una dosis de 5-10 ml IM cada 4-6 meses a personas en alto riesgo como es el caso de enfermos mentales recluidos en instituciones, donde a pesar de todas las medidas de higiene resulta difícil prevenir enfermedades como ésta. Este mismo preparado puede administrarse hasta 6 semanas después de una exposición a hepatitis A siempre y cuando no haya surgido aún evidencia clínica de la enfermedad. La dosis en este último caso varía de acuerdo al peso del individuo: 0.5 ml si es menor de 50 libras, 1 ml: 50-100 lbs., 2 ml, más de 100 lbs.

Las personas con anticuerpos anti-HA no necesitan esta profilaxis. Los efectos secundarios son poco frecuentes y van desde dolor e hinchazón local hasta reacción anafiláctica que afortunadamente es rara (42, 79, 80, 83).

En el estudio de Levy solo uno de los 202 contactos que recibieron la inmunoglobulina sérica desarrolló hepatitis y por el contrario cuatro de 32 que no la recibieron desarrollaron la enfermedad (35). La utilidad de la profilaxis con inmunoglobulina en la hepatitis A ha sido comprobada en otros estudios (37-39). Los estudios hechos demuestran que cuando el paciente de hepatitis A es hospitalizado ya la eliminación del virus en la excreta es mínima o inexistente (1). Por ello las precauciones a tomarse cuando se brega con un paciente de hepatitis A en el hospital son las mismas que se requieren para cualquier paciente hospitalizado (81). Véase Tabla IV.

Conclusión

Aunque la alta incidencia de anticuerpos circulantes contra hepatitis A en los distintos grupos de nuestro estudio podría ser explicada en base a factores como edad y nivel socioeconómico tenemos que preguntarnos si existen otros factores sobre los cuales podríamos ejercer alguna acción positiva. Debemos hacer todo el esfuerzo necesario para detectar cualquier posible foco clínico o subclínico en nuestro ambiente, ya que contamos con medidas profilácticas de interrupción de posibles brotes que ya han probado su eficacia.

Hepatitis B (hepatitis sérica)

El número de casos de hepatitis B reportados al CDC en Estados Unidos en 1978 fue de 15,016 (7). Al igual que con la hepatitis A hay una cantidad de casos no reportados o no diagnosticados (2). Aun con la tecnología rutinaria de detección del antígeno australiano escapan del diagnóstico algunos pacientes. En un estudio hecho en Suecia resultó que un 6.2 por ciento de pacientes negativos en la

prueba de HBsAg tenían infección diagnosticada por Anti-HBc (27).

El virus de la hepatitis B o partícula de Dane es un virus de 44 nanómetros el cual tiene tres antígenos: HBsAg, (antígeno australiano o de superficie), HBcAg (antígeno medular "core") y HBeAg (antígeno e). En adición a esto se conocen cuatro subtipos de HbsAg: adw, ayw, adr y ayr los cuales tienen valor epidemiológico. La partícula de Dane también contiene una enzima específica o polimerasa del DNA. Para cada uno de los tres antígenos mencionados existe un anticuerpo correspondiente: anti-HBc, anti-HBe y anti-HBs. La hepatitis B se transmite fundamentalmente a través de la sangre y sus derivados (40-42). El antígeno australiano se ha encontrado en excreta, orina, saliva, semen, líquido cefalorraquídeo, pero solo suero, saliva y semen han sido vinculados experimentalmente a la transmisión de hepatitis B (43). Es relativamente común la transmisión entre homosexuales, pero no existen datos que puedan afirmar cual es la ruta de contagio (44). Lo mismo sucede con el problema de la hepatitis sérica neonatal (45). Otro grupo de individuos con mayor incidencia de hepatitis B que la población control es el del personal que trabaja en el cuidado de enfermos en diversas instituciones tales como hospitales y asilos (46).

La hepatitis B tiene un período de incubación entre 4 y 28 semanas y su curso clínico individual es en la mayoría de los casos indistinguible del curso de la hepatitis infecciosa (47, 75, 76). Su severidad es variable y la mayoría de las veces evoluciona de forma subclínica (48). Sin embargo, la hepatitis B puede tener otras variantes en su evolución como hepatitis crónica y hepatitis fulminante (49, 50). También ha sido vinculada con cirrosis postnecrótica, carcinoma hepatocelular y enfermedad por complejos inmunes (glomerulonefritis, periarteritis nodosa) (51).

El diagnóstico de hepatitis B se hace rutinariamente por detección del antígeno australiano en la sangre del paciente. Este antígeno así como el HBeAg aparecen antes que los síntomas y la elevación de transaminasas. Con la aparición de los síntomas empieza a disminuir el nivel de estos antígenos que desaparecen por completo junto a las transaminasas (75). Cerca de 10 por ciento de las per-

sonas que sufren este tipo de hepatitis se convierten en portadores crónicos donde persiste positivo el HBsAg por años o de por vida (1). Estas personas pueden transmitir la enfermedad y están expuestas a desarrollar hepatitis crónica activa, cirrosis postnecrótica, cáncer de hígado y enfermedad por complejos inmunes (49-51).

Los anticuerpos contra antígeno c, antígeno e y el antígeno s surgen al final del cuadro clínico en ese orden aumentando en la convalecencia (75). Tabla III. El anti-HBs es señal de recuperación, ya que al parecer tiene un efecto protector contra el HBsAg (54, 76). A veces el HBsAg no se detecta aunque haya enfermedad y es aquí donde resulta útil el anti-HBc como prueba diagnóstica (27, 54). En cuanto al antígeno e, no se ha probado tenga significado pronóstico como una vez se creyó, sin embargo, se asocia con el grado de infectividad de la sangre del sujeto que lo posee (83).

Hepatitis B y hemodiálisis

La incidencia de hepatitis B en el paciente de hemodiálisis y en el personal a su cargo ha sido siempre notable. Es tal la importancia que reviste que es norma de todo hospital que tenga este servicio el hacer monitoreo de pruebas de función hepática y de antígeno australiano a todo paciente y personal. En un estudio hecho por Pattison en cuatro unidades de hemodiálisis un 34 por ciento de los pacientes y 36 por ciento del personal fueron HBsAg positivos, anti-HBs positivos o ambos (55). Un 13 por ciento de los familiares de esos pacientes mostraron positividad en la prueba de anti-HBs, siendo las esposas de los seropositivos las que más riesgo confrontaban. Otro estudio hecho por Szmuness en 15 centros de hemodiálisis en Estados Unidos demostró que de un total de 583 pacientes, 16.8 por ciento eran positivos para HBsAg y 34 por ciento eran positivos para anti-HBs. El personal a cargo de esos pacientes (total 451) eran positivos, 2.4 por ciento y 31.3 por ciento para HBsAg y anti-HBs respectivamente (56). La positividad de uno de los dos marcadores (HBsAg o anti-HBs) para los contactos familiares fue de 61 por ciento en aquellos pacientes

con historial de hepatitis. En este estudio se encontró relación con el tiempo en hemodiálisis, pero no con el número de transfusiones de sangre recibidas. En cuanto al personal no hubo diferencias relacionadas al tipo de labor por ellos realizada. Se postula que la mayor incidencia de antigenemia en pacientes en relación al personal puede explicarse por la diferencia en el sistema inmune. Para el paciente de hemodiálisis la transmisión parenteral (transfusiones, agujas contaminadas, salpicaduras de sangre, etc.) parece jugar un papel importante. Para el personal además del pinchazo accidental, tan frecuente en estos casos, parece tener importancia la transmisión no parenteral. Esto queda respaldado por el hecho de que no parece aumentar la positividad con el tipo de labor realizada, ni con el tiempo en el empleo. Un estudio reciente demostró que las superficies de acero inoxidable de las máquinas de hemodiálisis frecuentemente se manchan con sangre de los pacientes. A condiciones constantes (temperatura 25 C, humedad relativa 42 por ciento) esas manchas de sangre conservan 80-85 por ciento de su actividad antigénica al cabo de 14 días. Este estudio demostró también que el "swab" de algodón recogía el HBsAg en un 100 por ciento de los casos lo que lo hace ser un buen marcador epidemiológico (57).

En nuestro estudio los resultados son similares. La existencia de HBsAg en dos pacientes de hemodiálisis (4 por ciento) sin sintomatología ni evidencia alguna de hepatitis viral sugiere antigenemia crónica. De estos, uno fue anti-HBs positivo y otro negativo lo que sugiere un diferente estado inmunológico en ambos pacientes. En el personal no se encontró HBsAg positivo. De ser lo contrario serían necesarias ciertas medidas de control dado que un empleado portador crónico puede ser el origen de un brote de hepatitis B en cualquier momento. Aunque la positividad de anti-HBs fue de 30 por ciento en los pacientes versus 17 por ciento en los empleados al ver el número absoluto de pacientes y empleados resalta el hecho de que la incidencia es superior en los primeros (16 vs. 3).

Hepatitis B y el trasplante renal

Otra faceta que relaciona al paciente renal

TABLA IV

Precauciones en el Paciente de Hepatitis A Hospitalizado

-
1. Cuarto privado solo si hay incontinencia de heces fecales como en los niños pequeños.
 2. Lavado riguroso de las manos.
 3. Guantes al bregar con excreta, u objetos personales del paciente y al hacer la limpieza.
 4. Bata y mascarilla solo si se espera haya salpicadura de excreta (procedimiento).
 5. Desinfección de equipo médico y ropa.
 6. Excreta y orina directamente al inodoro o uso pato individual.
 7. Limpieza y desinfección de superficie contaminada.
 8. Identificación de especímenes de laboratorio.
-

con la hepatitis viral es el grupo de los transplantados. Los trabajos de Pirson tratan de determinar el efecto a largo plazo de la presencia de HBsAg en la evolución del paciente transplantado y la conservación del órgano recibido (58). Al seguir 172 pacientes con 188 órganos transplantados (14 de vivos y 174 de cadáveres) encontraron que hasta dos años del trasplante al antígenemia no tuvo efecto alguno sobre el órgano o el paciente, pero sí la tuvo después de los primeros tres años. Anteriormente, Charterjee había concluido que no había efecto adverso de parte de la antígenemia al menos hasta dos años que duró su estudio (59). Hillis recientemente hizo otro estudio y concluyó que después de nueve meses de hecho el trasplante, el número de muertes es mayor, pero solo 20 por ciento eran debido a fracaso hepático y el resto a otras infecciones y/o problemas cardíacos (60). Este grupo intenta correlacionar la antígenemia persistente con un grado pobre de inmunidad que hace al paciente víctima fácil de otras enfermedades. Aunque nuestro estudio no incluyó pacientes de trasplantes, es menester hacerse la siguiente pregunta: ¿Son los

pacientes renales HBsAg-positivo-persistente buenos candidatos para trasplante?

Prince evalúa el efecto de profilaxis con tres preparaciones de inmunoglobulina sérica con diferentes títulos de anti-HBs en 318 pacientes nuevos y 296 miembros del personal de hemodiálisis (61). Hubo 90 casos de hepatitis clínica o de HBsAg positivo, de los cuales 57 eran pacientes y 33 empleados. De ellos 46 y 31 eran Hepatitis B. Tanto para los pacientes como para los empleados la incidencia de hepatitis B fue menor en los que usaron HBIG que en los que usaron ISG. Los efectos adversos fueron mínimos, 5 entre 1,066 inyecciones puestas. A pesar de que el uso de estos productos parece tener un gran futuro no debemos olvidar que nada substituye al cuidado, la higiene y el uso de guantes al establecer la relación paciente-personal. Es importante señalar que la persona que está a cargo de la limpieza también está expuesto al contagio por lo cual debe protegerse e incluirse en el sistema rutinario de control.

Hepatitis B y Odontología

El dentista es uno de los individuos más ex-

puestos a desarrollar hepatitis sérica y a su vez puede ser el origen de posibles brotes epidémicos. Un caso ilustrativo presentado por Rimland analiza 71 pacientes en cinco condados en Estados Unidos que fueron atendidos por un mismo dentista entre dos a seis meses antes de que desarrollaron hepatitis B (62). De estos, 55 (79 por ciento) fueron contagiados por ese dentista que era portador crónico de HBsAg. En este análisis se concluyó que el mecanismo de transmisión fue hemo-oral. Mosley hace un estudio entre 1,245 dentistas durante una convención nacional en 1972 (63). Entre ellos hubo 11 casos positivos de HBsAg (0.9 por ciento) y 158 positivos para anti-HBs (12.7 por ciento). Noventa (7.2 por ciento) tenían historial de hepatitis icterica y de ellos 32 la sufrieron durante su práctica profesional. La incidencia era mayor cuanto más tiempo llevaban ejerciendo. Solo 13.1 por ciento acostumbraba a usar mascarillas y solo 6 por ciento usó guantes. El estudio de subtipos virales descartó la población de adictos como fuente de contagio. Otros estudios señalan que los dentistas sufren pinchazos más de una vez por semana. Feldman demuestra en su estudio una incidencia de hepatitis B de 6.7 por ciento en dentistas versus 2.4 por ciento en abogados (64). En este estudio sí fue significativo los datos de adictos como fuente de contagio. Williams estudia prospectivamente la posibilidad de contagio, a partir de un dentista portador (65). Este autor siguió a dos dentistas durante seis meses sin poder objetivar transmisión alguna a sus pacientes. La posible utilización de medidas preventivas (guantes, mascarillas) en estos dos dentistas conscientes de su condición hace que el estudio tenga poca validez. Merece la pena citar los trabajos de Villarejos donde se detecta HBsAg en la saliva del 76 por ciento de los pacientes durante las primeras semanas de los síntomas de hepatitis y del 86 por ciento de los portadores crónicos (en forma intermitente) (66). Parece ser que la saliva es el medio extraparenteral de transmisión de la hepatitis B. La rápida presencia de anti-HBs en la saliva quizás evite que la transmisión por este medio sea frecuente.

Nuestro estudio incluyó pocas personas relacionadas a la profesión de odontología para poder llegar a conclusiones objetivas. Sin embargo, la presencia de un caso HBsAg positivo (5 por ciento) y

2 casos anti-HBs positivo (9.5 por ciento) en un total de 21 es un dato a tenerse en consideración. Creo personalmente que el dentista y en particular el cirujano dental deben protegerse usando mascarilla y guantes. También pienso que estas personas deben hacerse con cierta periodicidad análisis serológicos. Solo de esta forma estarán sus pacientes y sus compañeros de labor protegidos.

Hepatitis B, el cirujano general y otro personal paramédico

El cirujano tiene un alto riesgo de adquirir hepatitis sérica. El trabajo de Rosenberg sobre cuatro cirujanos que operan un mismo paciente HBsAg positivo lo pone en evidencia (67). Estos cirujanos admitieron que en la cirugía mayor la ruptura de sus guantes es un hecho común particularmente cuando se brega con alambre de sutura.

Son numerosos los reportes que revelan el riesgo de la población médica y paramédica en relación con la hepatitis B. Snydman reporta un brote que tuvo su origen en una terapeuta de inhalación con dermatitis en sus manos y que manipulaba la cánula arterial desde un portador para obtener gases arteriales (68). Recientemente un grupo de 18 personas en nuestro hospital en su mayoría enfermeras tuvieron contacto directo con un paciente que murió de enfermedad hepática aguda y que poco antes de morir convirtió a positivo el HBsAg. Las 18 personas resultaron HBsAg negativos y 17 anti-HBs positivo.

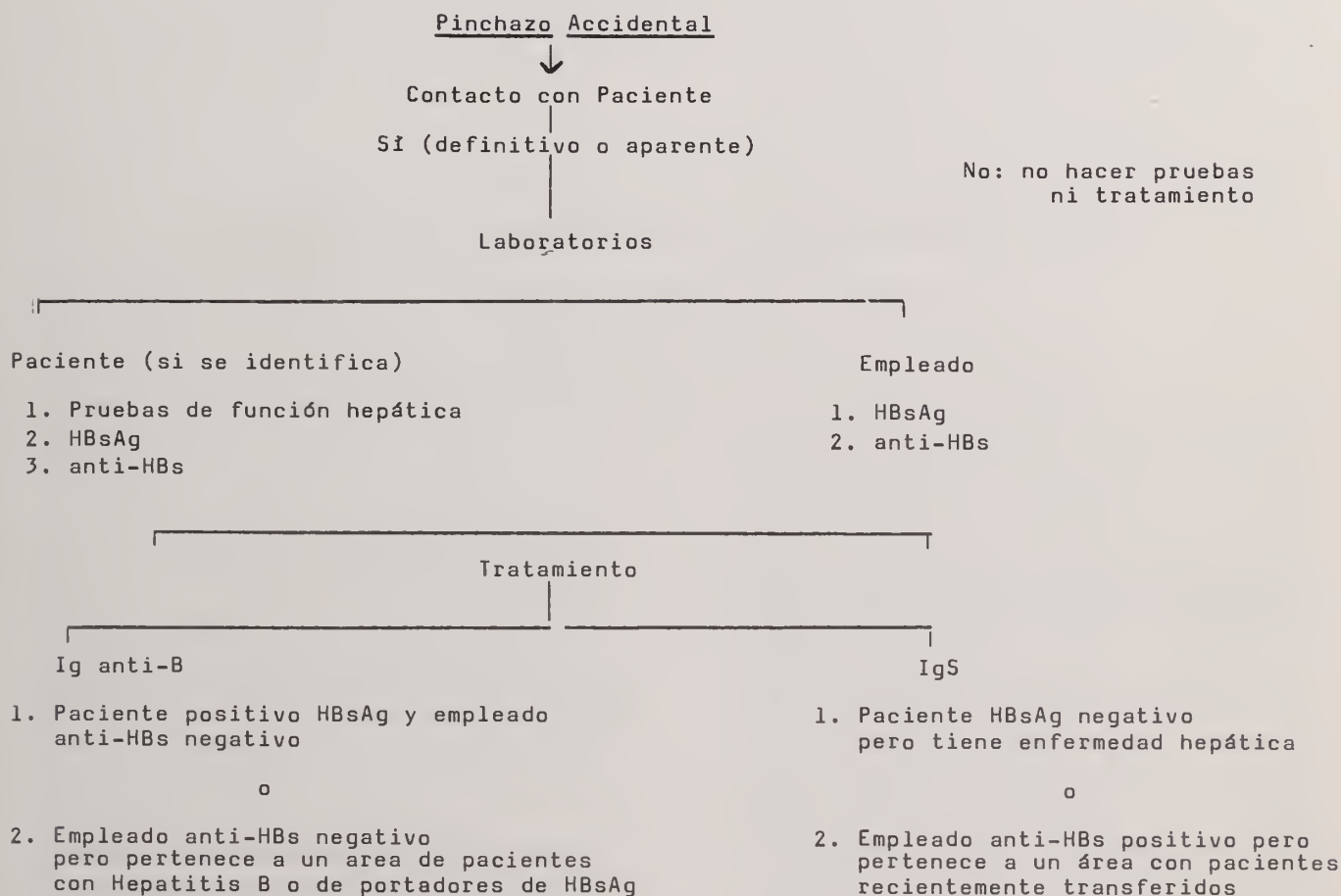
Esto ilustra el alto grado de exposición del personal paramédico en su trabajo ya que estas personas tenían inmunidad previa contra el virus de la hepatitis sérica.

Hepatitis B y los Tecnólogos Médicos

Basta una dilución de 1:10,000,000 de sangre para que esta pueda transmitir la hepatitis sérica (69). Este hecho dirige nuestra atención hacia aquel empleado del hospital que aunque no necesariamente establece contacto directo con el pacien-

TABLA V

Manejo del Empleado que Sufre un Pinchazo o Herida Accidental



te sí se relaciona de forma indirecta con él. Me refiero al personal del laboratorio clínico. En relación con esto hay que citar el estudio de Patisson sobre un brote de 5 casos de hepatitis B en un hospital de 500 camas en Phoenix, Arizona (70). Cuatro de estos pacientes sangraban frecuentemente y el otro era distribuidor. Ninguno era adicto ni había recibido transfusiones de sangre. El personal a cargo del laboratorio de investigación también está expuesto a esta enfermedad. Esto se ilustra en el estudio de Sutnick de un brote de cuatro casos clínicos y otros 15 sub-clínicos (estos últimos no confirmados) (70).

En nuestro estudio ningún miembro del laboratorio clínico resultó HBsAg positivo, sin embargo, hubo 5 casos (16.6) de anti-HBs positivo lo que evidencia enfermedad previa probablemente sub-clínica. Aunque el personal del laboratorio está consciente de este riesgo al manipular muestras de sangre o sangrar a los pacientes lo volvemos a recordar dada su importancia.

Hepatitis B y el Donante de Sangre

Años atrás una forma fácil de adquirir he-

TABLA VI

Precauciones en el Paciente de Hepatitis B o No-A, No-B Hospitalizado

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1. Lavado de manos.
 2. Guantes al bregar con sangre o sus derivados. Si hay dermatitis, siempre.
 3. Desinfectar el equipo médico contaminado con sangre así como objetos personales.
 4. Uso de jeringuillas y agujas desechables, no manipularlos.
 5. Cuidado y rotulación de especímenes de laboratorio.
-

patitis sérica era a través de transfusiones de sangre contaminada con el virus. Los factores que han reducido a 13 por ciento la incidencia de hepatitis B post-transfusional son los siguientes: 1) muestra rutinaria de HBsAg, 2) uso de sangre de voluntarios, 3) progreso en la metodología de identificación de HBsAg (40). La incidencia de hepatitis post-transfusión es aún de 8-45 por ciento de acuerdo a varios estudios, sin embargo, se estima que el virus más frecuente es el de la hepatitis No-A, no-B ocupando un 40-71 por ciento de los casos (72). El uso de proplex un concentrado de factor IX en pacientes de cirugía cardíaca originó un 13.8 por ciento de hepatitis B en los que los recibieron y cero en el grupo control aunque previo a su uso el concentrado resultó negativo para HBsAg (73). El método de congelación y degliceración de la sangre previo a su administración no eliminaba de ésta el factor HBsAg (74). Cualquier producto de sangre puede potencialmente transmitir el virus de la hepatitis B.

Nuestro estudio incluyó 78 donantes de sangre, todos ellos HBsAg negativos. Trece de ellos (17 por ciento) tenían anti-HBs positivo lo que sugiere infección previa pero elimina el estadio de portador y la infección activa.

Inmunoglobulina anti-B

La inmunoglobulina anti B es una inmunoglobulina que reúne títulos altos de anticuerpos contra el virus de la hepatitis B. Su precio es de \$150.00 por cada inyección, aunque esto es variable.

La Tabla V nos describe la conducta a seguir en el caso tan frecuente del pinchazo accidental del empleado del hospital con agujas o algún otro material que se sospecha puede estar contaminado. La dosis óptima post-exposición no se conoce a ciencia cierta, pero los estudios hechos sugieren 0.07 ml/kg a administrarse no más tardar de 7 días después del pinchazo. Solo en el caso especial de un individuo expuesto de forma continua y con gran riesgo (personal de hemodiálisis) debe considerarse el uso de este preparado en pre-exposición administrando 5-10 ml cada 4 meses. Los efectos secundarios de la inmunoglobulina anti-B son poco frecuentes y usualmente transitorios. Se puede esperar reacción inflamatoria local y en muy raras ocasiones anafilaxis (42, 80, 83). Individuos con HBsAg positivo, anti-HBs positivo o anti-HBc positivo no deben ser vacunados. La presencia de anticuerpos es índice de protección.

Cuando se hospitaliza un paciente con hepatitis B deben tomarse ciertas precauciones las cuales se enumeran en la Tabla VI. Estas son similares a las que se toman en caso de hepatitis no-A, no-B (81). Existe el problema de que muchos hospitales no cuentan con facilidades que permitan hacer diagnóstico específico del tipo de hepatitis viral. En estos casos es necesario tomar precauciones de índole gastroentérico y de sangre.

Merece la pena citar el estudio prospectivo de Grady y colaboradores donde 172 individuos expuestos a sangre de pacientes con HbsAg positivo son randomizados y reciben profilaxis con ISG con diferentes títulos de anti-HBs: bajo = 1:50, intermedio = 1:5,000 y alto = 1:500,000. Hubo 39 casos de hepatitis aguda y se confirmó Hepatitis B en 34 de ellos. De los 39 casos de hepatitis aguda 7 por ciento habían recibido profilaxis con título de 1:50, 5 por ciento con título de 1:5,000 y solo 2 por ciento con título de 1:500,000. La diferencia fue significativa entre los grupos de bajo y alto título, pero no lo fue entre el de alto e intermedio. Los efectos secundarios como reacciones locales de dolor e hinchazón o rash y las generales con hipotensión, urticaria y síncope fueron poco frecuentes (1.6 por ciento) y transitorias. Estos autores recomiendan el uso de globulina sérica con títulos intermedios de anti HBs para la profilaxis de Hepatitis B en sujetos expuestos a pacientes con HBsAg positivo (80).

Seeff y col. evaluaron 302 sujetos y determinaron que HBIG reducía significativamente la frecuencia de hepatitis B clínica o subclínica durante los primeros cuatro meses después de administrada. Este estudio sugiere la necesidad de administración de HBIG cada cuatro meses en aquellos individuos expuestos de forma continua (83). Estos mismos autores, en un estudio ulterior, demuestran que existe una diferencia significativa al usar HBIG (anti-HBs = 1,100,000) en lugar de ISG (menos de 1:8 de anti-HBs) en la profilaxis de hepatitis B después del pinchazo accidental (42). Tres sujetos de 216 (1.4 por ciento) que recibieron HBIG (1:100,000) y 12 sujetos de 203 (5.9 por ciento) que recibieron ISG desarrollaron hepatitis B.

Conclusión

La transmisión del virus de la hepatitis B

está íntimamente ligada a las diferentes actividades del médico y del personal paramédico. Sin embargo, el diagnóstico temprano de hepatitis B es cada día más factible y con ello la puesta en práctica de medidas preventivas como la precaución con todo producto de sangre y la forma moderna a base del uso de HBIG (79). Teniendo en cuenta la gran cantidad de hepatitis sub-clínicas que pasan desapercibidas y el hecho de que la sensibilidad de los medios diagnósticos comúnmente en uso no es perfecta debemos ser cautos desde el preciso momento que iniciamos nuestra labor diaria en el hospital.

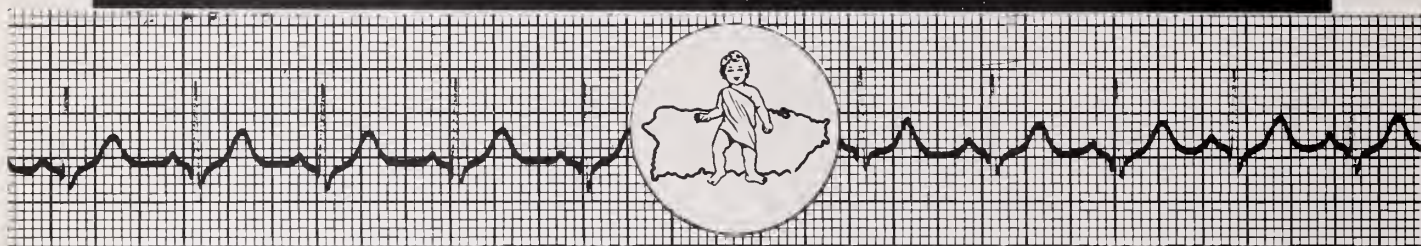
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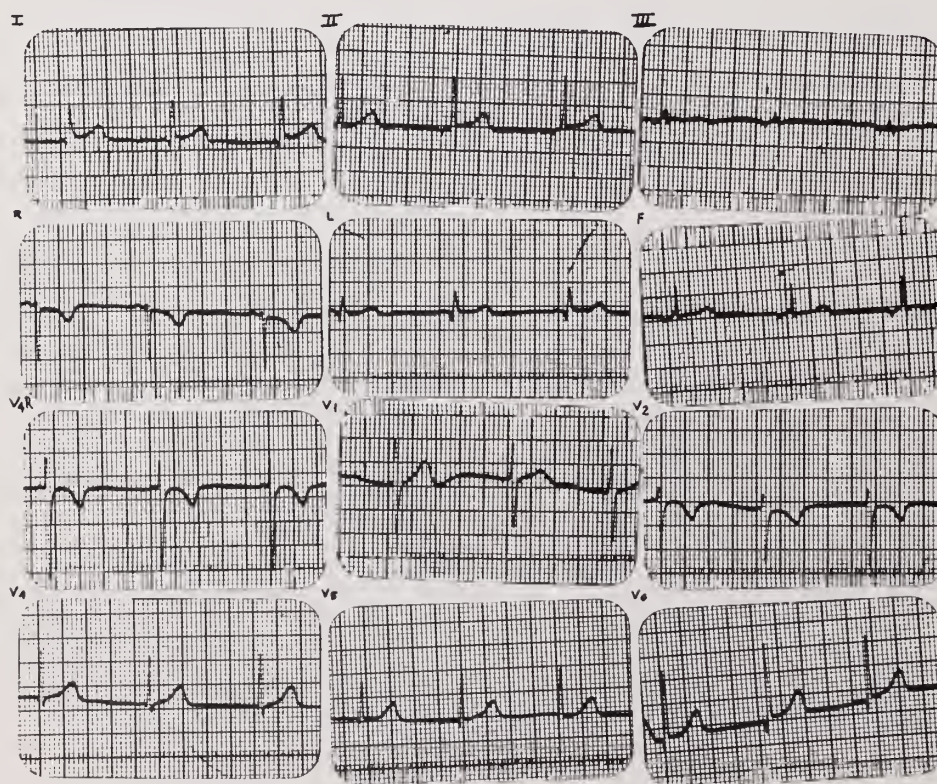
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CASOS DE ELECTROCARDIOGRAFIA PEDIATRICA



Rafael Villavicencio, MD

Un paciente de 10 años es referido para evaluación por un soplo detectado durante un examen de rutina reciente. El niño estaba asintomático, y el examen físico solo demostraba un niño delgado, con un soplo funcional. La radiografía de torax era negativa, y se obtuvo el electrocardiograma que se ilustra a continuación:



El trazado electrocardiográfico demuestra:

- a) Prematuro atriales
- b) Dextrocardia
- c) Ritmo nodal alto
- d) Ritmo sinusal
- e) Bloqueo atrio-ventricular

Respuesta: C Ritmo Nodal ("Junctional Rythm")

En el ritmo nodal las ondas P son negativas en L₂, L₃, aVF, y positivas en aVR. El intervalo PR es usualmente corto, y tanto el segmento QRS como la onda T son de configuración normal. En el caso del ritmo nodal alto (trazado) la secuencia P-QRS es normal (1).

Mecanismo

Al originarse el impulso en el nódulo atrioventricular (AV), éste se propaga de forma anterógrada a los ventrículos y retrógrada a los atrios. Por consiguiente, las ondas P resultantes tendrán una dirección opuesta a las que se originan en el nódulo sinusal.

Según el punto de origen del estímulo en el nódulo AV puede variar la secuencia P-QRS en el ritmo nodal. Si el estímulo se origina en la parte alta del nódulo la secuencia P-QRS será normal. Si es en la porción media la onda P estará ausente, pues coincide con el QRS. Cuando el estímulo procede de la porción baja del nódulo AV la onda P le sigue al segmento QRS (2).

Causas

En niños el ritmo nodal puede estar presente en:

- 1) corazón normal
- 2) miocarditis
- 3) desbalance electrolítico, hipoxia
- 4) post cirugía cardíaca-sobre todo en cirugía atrial y en la corrección de la transposición de los grandes vasos.
- 5) vagotonía

Tratamiento

Si la frecuencia ventricular es normal, el ritmo nodal no requiere tratamiento.

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ELECTROCARDIOGRAM OF THE MONTH

Rafael A. Cox, MD and Charles D. Johnson, MD

Case Report

The electrocardiogram (ECG), Figures 1 and 2, was performed (2-10-81) on a 91-year-old male with history of arterial hypertension and left-sided heart failure of several years duration, for which he was on Digoxin 0.25 mg daily, Lasix 20 mg. twice daily and potassium replacement. He was referred to our institution on 2-5-81 after having a fall in which he sustained a left intertrochanteric femoral fracture. As he was subsequently found with pre-renal azotemia and uncontrolled blood pressure, surgery was cancelled and he was transferred to our Medicine Department.

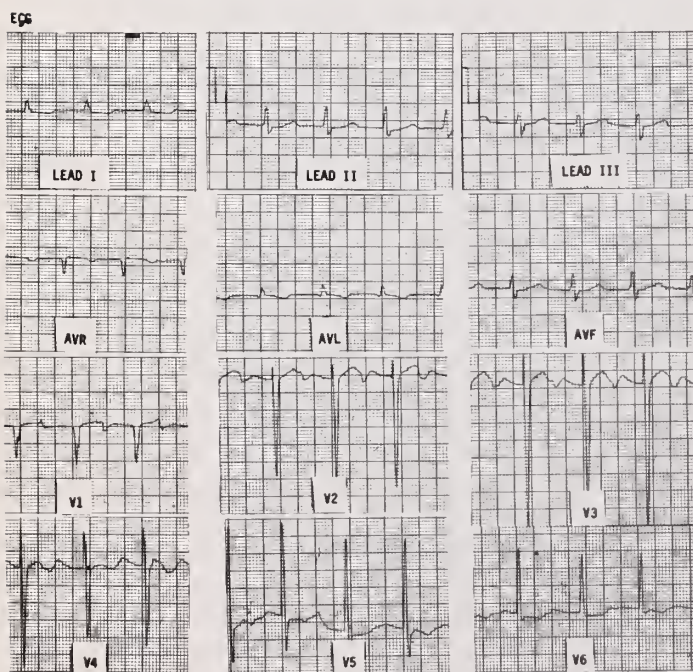


FIG. 1

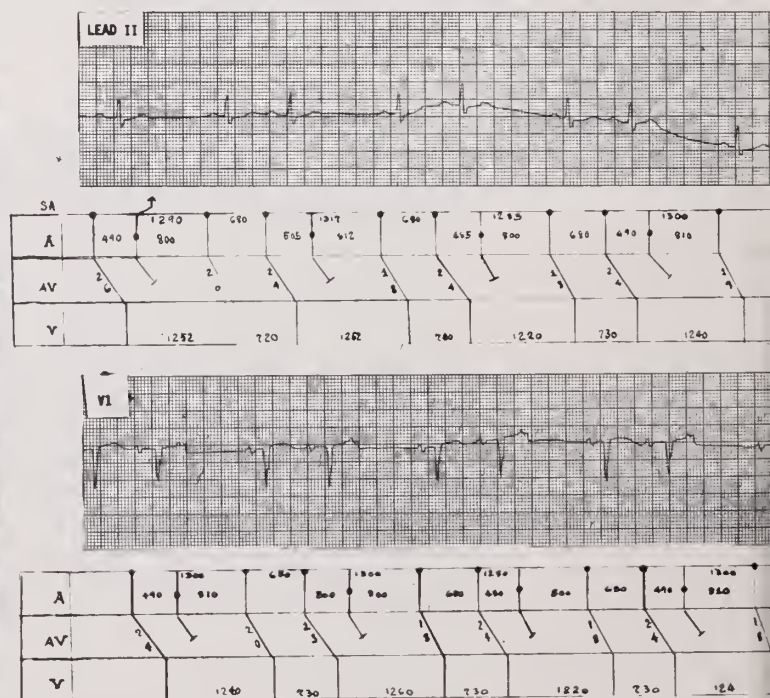


FIG. 2

Questions

- 1) Study the electrocardiograms
- 2) What are the electrocardiographic diagnoses?
- 3) What is the cardiac arrhythmia?
- 4) What is the pathogenic electrophysiology of the arrhythmias?

Answers. Interpretation of the ECG's

Normal sinus rhythm.

Type I second degree (Wenckebach) conduction

Nonconducted unifocal premature extrasystole, atrial premature contraction - APC - (P') in trigeminal rhythm.

The APC's interrupt Wenckebach periods.

Complete ECG (Figure 1) - Rate 88 per minute, P-R interval 0.40 S; QRS complex 0.09 S: axis + 15 degrees; P wave configuration differs in V₁; P waves of low voltage in many leads; Q wave in aVL; ST segments depressed in leads 1, aVL, V₅₋₆ and T waves diphasic in leads 1, aVL, V₅₋₆; prominent T &/or U waves in V₂₋₄. Normal sinus rhythm, biatrial enlargement, left ventricular hypertrophy, first degree atrioventricular (AV) block, ST-T wave abnormalities, and two APC's (V₄, V₅).

Diagrammed Rhythm Strips (Figure 2). - Normal sinus rhythm is present at a rate of 88 per minute (P-P interval = 680 mS). The third atrial deflection (P') is different, premature, pointed and superimposed on the preceding T wave. It appears to be upright in both leads II and V₁. Its coupling interval is constant, the P-P interval = 480-505 mS. The ensuing P'-P intervals = 800-812 mS, which represent an incomplete compensatory pause (the P - P interval surrounding the APC, pre and post, measure 1280-1317 mS and is smaller than two times the basic sinus interval of 1360 mS, i. e. 2 x 680 mS). However, the P' - P interval of 800-812 mS is greater than the basic sinus interval of 680 mS. This is due to the APC reaching the sinus node and prematurely discharging it. This temporarily depresses its automaticity and lengthens its inherent cycle and the postextrasystolic pause (returning cycle). The pause may also be due to interference within the sinoatrial node or junction because of the long refractory period in the sinus node from the preceding basic sinus impulse discharged. The R - P' intervals measure 240-265 mS. The shorter R - R intervals measure 720-740 mS and the longer ones 1220-1260 mS. The calculated sinus cycle =

$$\frac{\text{Isoconduction Interval (II)}}{\text{Number of R - R intervals in II} + 1} = \frac{R_1 \dots R_3}{2 + 1} = \frac{1965}{3}$$

= 655 mS.

Electrophysiology

The early APC falls on the T wave and is not conducted because the AV junction is still in its absolute refractory period (physiological refractoriness rather than a pathological block). The

cardiac cycle length immediately preceding the APC's coupling interval is relatively long, as the duration of the cardiac cycle influences directly the refractory phase of the AV conduction tissues (Ashman phenomenon). These two electrophysiological laws underlie the nonconduction.

The nonconducted APC affords the AV junction a relatively long rest period. This favors the first postextrasystolic sinus impulse being conducted with a relatively short P-R interval of 0.18-0.20 S, whereas the second sinus impulse is conducted with a prolonged P-R interval of 0.23-0.26 seconds.

The nonconducted atrial extrasystole after every second conducted sinus beat manifests as an atrial trigeminal rhythm and ventricular bigeminal rhythm, and appears as an APC interrupting a Wenckebach period.

Wenckebach block is due to an abnormal prolongation to an equal or unequal degree of both the absolute and relative refractory periods of the AV junction.

Differential Diagnoses

1) Nonconducted APC -

- a. The P' has a different shape and size (contour) than that of the sinus P waves.
- b. The compensatory pause is usually incomplete.
- c. No accompanying QRS complex.

2) AV Junctional Extrasystole with antegrade nodal block and an incomplete compensatory pause.

- a. The P' wave is negative in leads II, III, aVF (- 60 to - 90 degrees; equiphasic or slightly positive P' in lead I) and is completely positive in V₁ with loss of the normal terminal negative P component.

3) Sinus Premature Extrasystoles

- a. Rare
- b. The P' wave, the QRS and T waves are identical to the normal sinus P and to the basic rhythm, respectively.
- c. Sudden abbreviation of the sinus cycle.
- d. The postextrasystolic compensatory pause is incomplete (no compensatory pause) and is identical to the P - P' interval during normal sinus rhythm at distinctly different rates of the normal sinus rhythm.
- e. Mostly present in a bigeminal pattern.

4) Marked Sinus Arrhythmia

- a. May be related to respiration.
- b. Irregular P - P cycle; variation in P - P interval of 0.16 S or more.

- c. Gradual increase or diminution of the P - P cycle lengths.
 - d. P wave of sinus origin.
 - e. The P configuration can vary slightly depending on the phase of respiration.
- 5) Sinus Arrest
- a. The P - P interval varies greatly. Its duration has no relation to the basic P - P interval.
- 6) 3:2 Sinoatrial Block of the Wenckebach type plus Wenckebach AV Conduction
- a. Gradual shortening of the P - P intervals, followed by a sudden long pause (when sequences are longer than 3:2).
 - b. The long P - P interval is less than the sum of twice the shorter P - P interval.
 - c. The third sinus impulse (and QRS complex) is blocked within the sinoatrial junction and thus not evident.
 - d. The P-R interval of the second conducted beat prolongs over that of the first beat.
 - e. The blocked P wave of Wenckebach AV block would not be premature and would be of basic sinus origin.
 - f. The AV Wenckebach pause equals 2 times the basic sinus cycle - sum of the P-R interval increments.
- 7) Atrial Reciprocal Rhythm or Atrial Echo Beat (Reversed Reciprocal Rhythm) plus AV Wenckebach phenomenon.
- a. A P-QRS-P' sandwich.
 - b. The QRS complex associated with the long P-R interval of the Wenckebach sequence is followed by a retrograde P' atrial activation (-90 to -110 degrees: negative P' in leads I, II, III, aVF, narrow pointed upright in V₁).
 - c. The P' waves are selectively linked to the long P-R intervals.
 - d. The P-R interval is usually long, and the R-P' usually short. (Schamroth)
 - e. The post echo pause, the P' - P interval is longer than the normal sinus cycle due to post-prematurity depression.

Wenckebach sequences ending in atrial reciprocal beats are indeed difficult to exclude in our case as the P' waves appear bifid and upright in V₁. However, the P' waves in lead II are probably upright and anterograde.

Similar examples have been published by Schamroth (Case 9, pp 340-341, Reference 7) and Chung (Figure 8-31, p 310, Reference 1; and Figure 8-66, pp 132 Reference 2).

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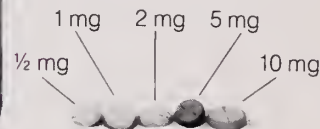
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Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity.

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticonvulsant medication since HALDOL haloperidol may lower the convulsive threshold; (3) with known allergies or a history of allergic reactions to drugs. Concomitant antiparkinson medication, if required, may have to be continued after HALDOL haloperidol is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time. The 1, 5, 10 mg tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Adverse Reactions: CNS Effects: Extrapyramidal Reactions. Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs. Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn.

Persistent Tardive Dyskinesia. Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by re-institution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms.

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis, agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice reported. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia and hypoglycemia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other neuroleptic drugs.

The injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

Caution: Federal law prohibits dispensing without prescription.

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IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

HALDOL tablets and concentrate (120 ml) are manufactured by McNeil Pharmaceutical Co., Dorado, PR 00646

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References:

1. Smith GR, et al. *Psychosomatics* 15: 134, 1974. 2. Tobin JM, et al. *Geriatrics* 25(6):119, 1970. 3. Bernstein JG. *Clinical Psychopharmacology*. Littleton, MA, PSG Publishing Company, 1978, p 123. 4. Stotsky BA, in DiMascio A, and Shader RI. *Butyrophenones in Psychiatry*. New York, Raven Press, 1972, p 71.

McNEIL PHARMACEUTICAL
McNEILAB, INC. · Spring House, PA 19477

Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Chemical Burns Can Damage Eyes

Eye Burns Serious

Chemical burns of the eye are very serious and may lead to blindness if immediate action is not taken. Speed in removing the burning chemical is all important. Drain cleaner, bleach or other cleaning solutions are some chemical agents that can burn the eye.

Flush the eye immediately with large quantities of cool running water for about ten minutes to rinse out the offending chemical. Hold the victim's head under a faucet, prop the eyelids open and allow the water to run from the inside (near the nose) to the outside. If both eyes are affected, let the water flow over both or quickly alternate from one eye to the other. Pull back eyelids so all parts of the eye will be cleansed.

The American Medical Association's Handbook of First Aid and Emergency Care suggest that if no faucet is available, fill a sink or large pan with water and have the victim immerse his face and blink frequently.

After flushing thoroughly, cover the injured eye with a pad of sterile gauze

or a clean folded handkerchief and bandage in place. Do not allow the victim to rub his eyes. Get medical attention promptly, preferably from an ophthalmologist, or at the nearest hospital emergency room.

Never attempt to remove a foreign body that is sticking to the eyeball. Particles of eyelashes or specks that are resting or floating on the eyeball or inside of the lid may be carefully removed.

If the foreign body is sticking to the eyeball or into the eye, let it alone and get medical attention promptly. If it is floating on the eyeball, gently pull upper eyelid down over lower eyelid and hold for a moment. This causes tears, which will hopefully wash out the particle.

If this doesn't work, fill a medicine dropper with warm water and flush out the particle. If this fails, carefully lift the particle out with a moistened corner of a clean handkerchief or cloth.

Any cuts to the eye can be very serious. Cover the injured eye with a sterile pad or gauze or clean folded cloth, bandage in place and get to a doctor quickly.

For a hard blow to the eye from a ball, fist, etc., apply cold compresses, keep the victim lying down if possible, and get to the doctor.



July, 1981
Frank Chappell
Science News Editor
AMA

Tolectin[®] DS

(TOLMETIN SODIUM) DOUBLE STRENGTH
CAPSULES 400 MG.

in action 





IN OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS*:

dependable control of arthritic symptoms

RAPIDLY CONTROLS INFLAMMATION RELIEVES STIFFNESS AND PAIN

- peak plasma levels reached within 30–60 minutes
- therapeutic response can be expected in a few days to a week
- improvement reported in 75% of 4,757 patients[†]

CONTINUED CONTROL FOR YEARS

- decrease in duration of morning stiffness²
- steady decline in mean number of inflamed joints³
- symptomatic control maintained over three years of therapy³

Tolectin[®] DS
(TOLMETIN SODIUM) DOUBLE STRENGTH
CAPSULES 400MG.

Convenient starting dose: usually 1 capsule t.i.d. with meals.

May be safely administered with other needed therapies: does not interfere with concomitant hypoglycemic¹ or anticoagulant⁴ medication.

⁴For patients classified as Functional Class IV (incapacitated with little or no self-care), safety and effectiveness have not yet been established.

[†]Includes patients with minimal, moderate, and marked response to therapy.

Please turn page for brief summary of prescribing information.

SUMMARY OF PRESCRIBING INFORMATION

TOLECTIN® DS (tolmetin sodium)

double-strength capsules—for oral administration

Description: *TOLECTIN DS* (tolmetin sodium) capsules contain tolmetin sodium as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium.

Contraindications: *Tolmetin* (tolmetin sodium) should not be used in patients who have previously exhibited intolerance to it or patients in whom aspirin and other non-steroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria.

Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported.

If *Tolmetin* must be given to patients with active peptic ulcer, closely supervise the patients for signs of ulcer perforation or severe gastrointestinal bleeding.

Precautions: *General*—Clinical studies of up to two years duration have shown no changes in the eyes attributable to *Tolmetin* (tolmetin sodium) administration, however, because of ocular changes observed clinically with other non-steroidal anti-inflammatory drugs, ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.

There has been no evidence of renal toxicity to date in clinical studies, however, since *Tolmetin* is eliminated primarily by the kidneys, closely monitor patients with impaired renal function; they may require lower doses.

Tolmetin prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when *Tolmetin* is administered.

In patients receiving concomitant *Tolmetin*-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

Tolmetin should be used with caution in patients with compromised cardiac function.

The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g. sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips (e.g. Albustix®, Uristix®, etc.).

Usage in Pregnancy—Since *Tolmetin* has not been studied in pregnant women, the use of *Tolmetin* during pregnancy is not recommended.

Nursing Mothers—Because *Tolmetin* may be secreted in human milk, as a general rule nursing should not be undertaken while a patient is on this drug.

Drug Interactions—Although *Tolmetin* has been found *in vitro* to bind extensively to plasma protein, it does not alter the dosage of warfarin required to maintain a uniform prothrombin time.

In adult diabetic patients under treatment with either sulfonylureas or insulin, there is no change in the clinical effects of either *Tolmetin* or the hypoglycemic agents.

Adverse Reactions: Gastrointestinal System—The most frequent adverse reactions which occurred were gastrointestinal: nausea, 1 in 9 patients, dyspepsia, 1 in 10 patients, abdominal pain, 1 in 15, gastrointestinal distress, 1 in 15, flatulence, 1 in 25, diarrhea, 1 in 25, constipation, 1 in 40, vomiting, 1 in 30, gastritis, 1 in 55, and significant gastrointestinal bleeding without evidence of peptic ulceration, 1 in 240.

The incidence of peptic ulcer in about 3000 patients treated up to two years in clinical studies was about 1 in 50. Thirty-four percent of the ulcer patients had prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs, including corticosteroids, known to produce peptic ulceration.

In clinical trials about 10% of patients dropped out because of adverse reactions, mostly gastrointestinal in nature.

Body as a Whole—headache, about 1 in 10 patients, asthenia and chest pain, less frequently, and, rarely, anaphylactoid reactions.

Cardiovascular—edema, about 1 in 15 patients; hypertension, less frequently.

Central Nervous System/Psychiatric—dizziness or lightheadedness, about 1 in 20 patients, tension or nervousness, 1 in 50 patients, drowsiness, 1 in 60 patients, insomnia and depression, less frequently.

Dermatologic—rash, about 1 in 40 patients, pruritus, 1 in 60 patients, skin irritation, 1 in 55 patients.

Special Senses—tinnitus, about 1 in 65 patients.

Hematologic—Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred. This is similar to that reported with other non-steroidal anti-inflammatory drugs. A few cases of granulocytopenia have been observed.

Caution: Federal law prohibits dispensing without a prescription.

Full directions for use should be read before administering or prescribing.

For information on symptoms and treatment of overdose, see full prescribing information.

Also available: *TOLECTIN*® (tolmetin sodium) tablets 200 mg. DEPOT STOCKED 500's Military 6505-01-030-3241 VA 6505-01-030-3241 A.

References: 1. Data on file, Medical Division, McNeil Pharmaceutical. 2. Reid RT, Levin J, Ricca LR, et al. Tolmetin sodium in the treatment of chronic osteoarthritis: an analysis of 725 patients with a year or more of therapy. *Curr Ther Res* 28:173-184, August 1980. 3. From a three-year, multi-clinic open evaluation of *Tolmetin* tolmetin sodium, involving 42 patients with rheumatoid arthritis. 4. Whitsett TL, Barry JP, Czerwinski AW, et al. Tolmetin and warfarin: A clinical investigation to determine if interaction exists, in Ward JR (ed) *Tolmetin, A New Non-Steroidal Anti-Inflammatory Agent. A Symposium*, Washington, DC April 1975. Princeton: Excerpta Medica, 1976. pp 134-141.

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AVISO DE INTERES

La Junta Editora, consciente de su responsabilidad de hacer que el "Boletín" cumpla a cabalidad con su cometido de divulgar conocimientos médicos, elevar las normas de educación médica y al propio tiempo de llenar las necesidades de todos los compañeros médicos, ha acordado establecer una nueva Sección que se conocerá como "Sección de Preguntas".

Bajo esta nueva Sección, todos los compañeros tendrán la oportunidad de enviarnos preguntas médicas de casos difíciles o casos clínicos para opinión experta. Estas preguntas, con sus respuestas, serán publicadas en esta nueva Sección.

Las preguntas deberán ser enviadas a:

Boletín de la AMPR
Sección de Preguntas
Apartado 9387
Santurce, P. R. 00908

Esperamos sus preguntas.

Juan M. Aranda, MD
Presidente
Junta Editora

GRAPHICS

Oswaldo Jiménez, MD, José Couto, MD y José Peguero, MD,
Cardiology Service, Veterans Administration Hospital, San Juan, P. R.

Paciente varón de 50 años de edad, viene a la sala de emergencia con dolor de pecho, retrosternal, al descanso, de varios minutos duración. Estos episodios ocurren desde hace 3 meses, usualmente por las mañanas. Niega antecedentes cardíacos y solo usaba teofilina para su asma bronquial. El electrocardiograma en la sala de emergencia fue el siguiente:

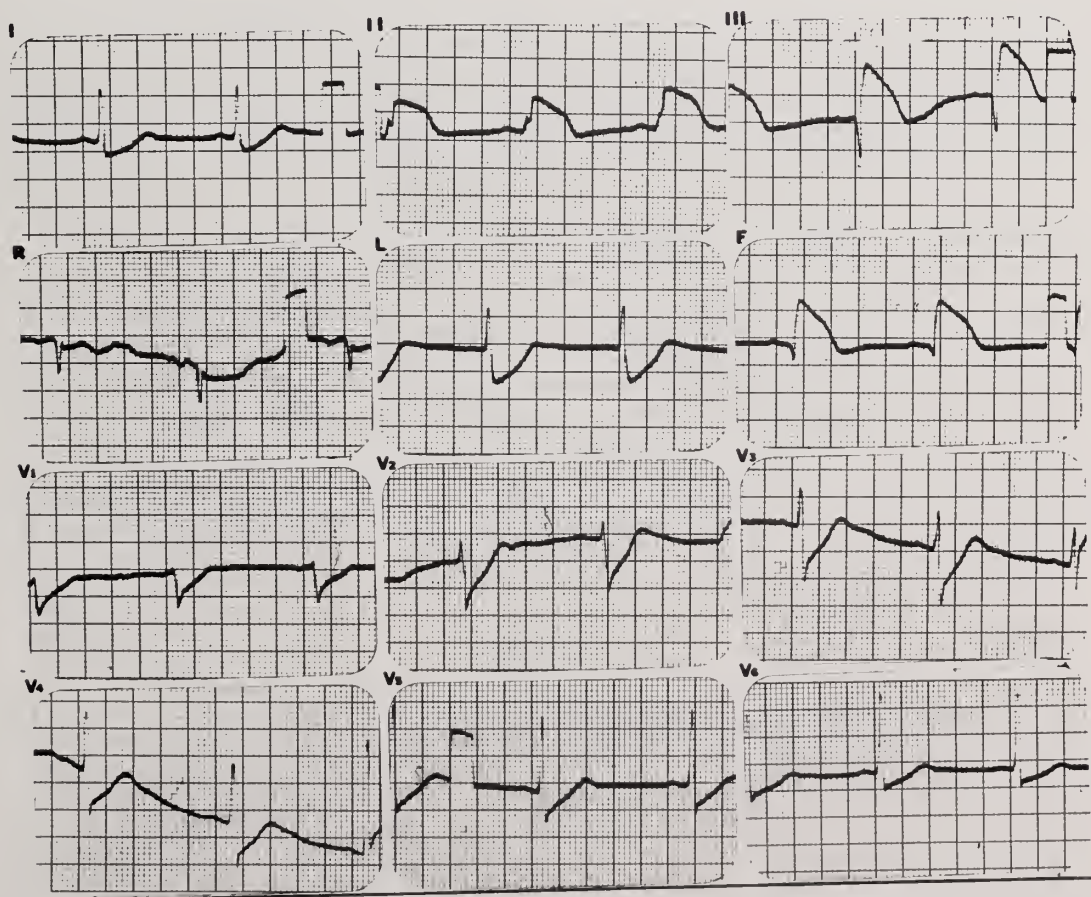


Figura 1

En la unidad de coronaria, se le repitió otro electrocardiograma 20 minutos más tarde.

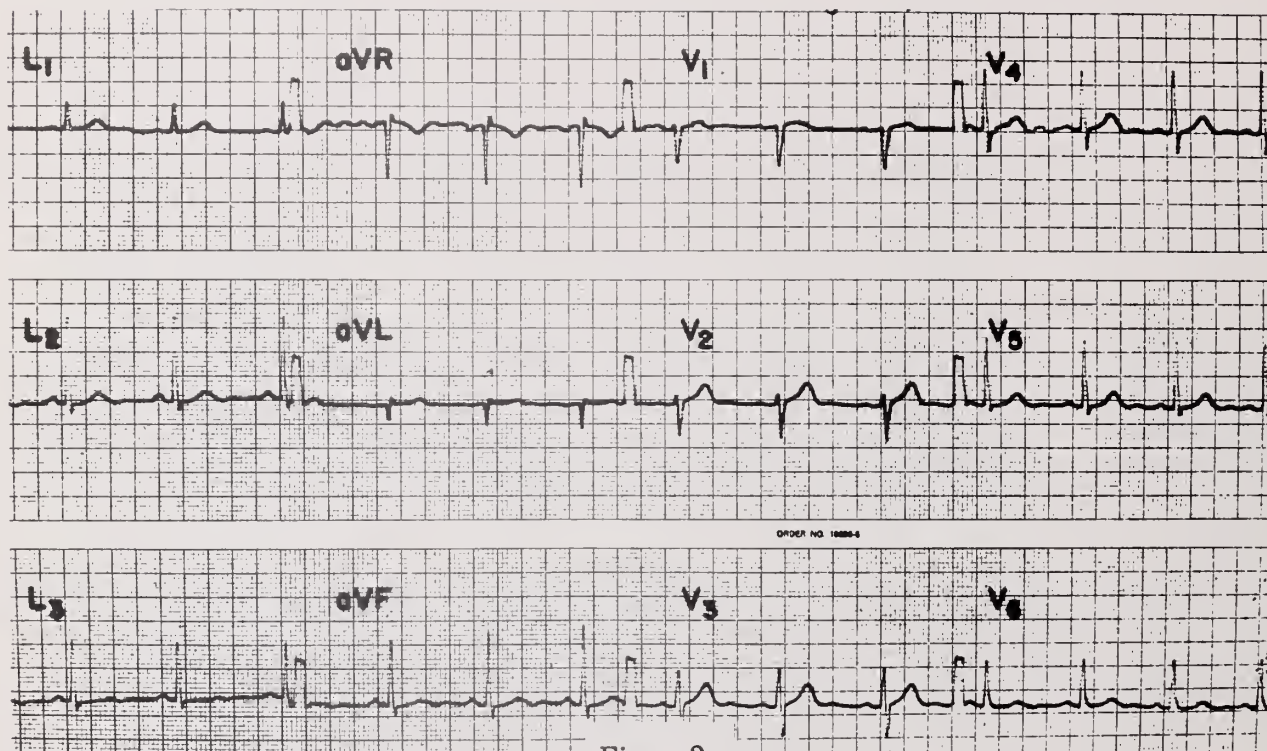


Figura 2

Estos dolores se repitieron en tres ocasiones. El trazado electrocardiográfico durante el dolor fue similar al ilustrado en la Figura 1.

Durante una prueba de ejercicio efectuada 4 semanas más tarde, se demostró lo siguiente:

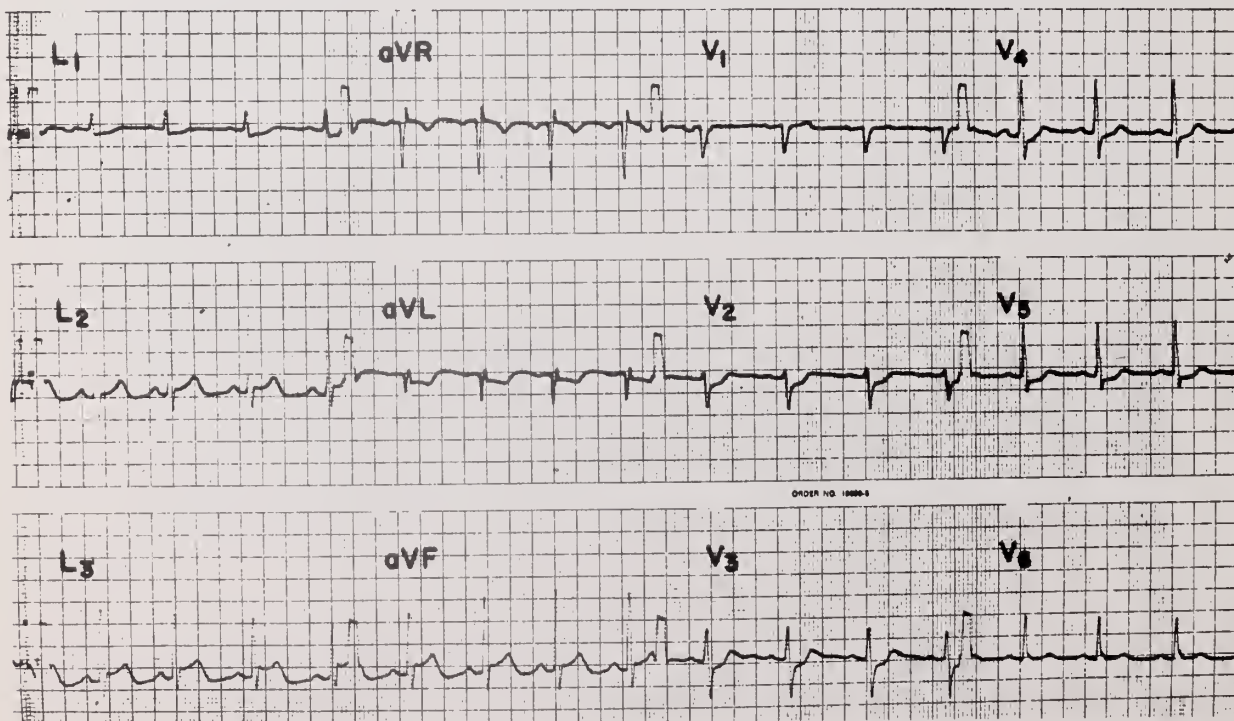


Figura 3

Los trazados electrocardiográficos son representativos de: (escoja la mejor contestación - puede haber más de una)

- a. Un infarto agudo con cambios residuales sería la explicación más lógica para explicar el cuadro clínico de este paciente.
- b. Un agente beta bloqueador selectivo es el medicamento de elección.
- c. La angina de Prinzmetal es el diagnóstico más probable; agentes vasodilatadores es el tratamiento recomendado.
- d. El uso de agentes bloqueadores de los canales lentos de calcio (Nifedipina) es el tratamiento de elección.

Contestaciones: c y d

Este es un caso representativo de vasoespasmo de una arteria coronaria descrita por Prinzmetal en el 1959. En el 60 por ciento de estos casos, el vasoespasmo está asociado a enfermedad obstructiva de las arterias coronarias. En algunos pacientes el vasoespasmo puede ser inducido por el ejercicio, aunque a la gran mayoría ocurre al descanso. El uso de propranolol es controversial. En los pacientes en que existe obstrucción arteriosclerótica coronariana concomitantemente, los beta bloqueadores al disminuir los requerimientos de oxígeno por el miocardio, podrían ser de utilidad.

Las arterias coronarias tienen receptores vasculares alfa y beta. Estimulación de los receptores alfa causan constricción de las arterias mientras que estimulación de los beta tiene como resultado vasodilatación de las mismas.

En los pacientes donde el espasmo no está asociado a enfermedad coronaria los beta bloqueadores permiten un predominio del efecto mediado a través de los receptores alfa. Como resultado podría aumentarse la frecuencia o intensidad del vasoespasmo.

Los agentes bloqueadores de los canales lentos de calcio de la célula miocárdica; Nifedipina, se han utilizado recientemente en la angina vasoespástica. El calcio junto a las prostoglandinas y el monophosphato de adenosina cíclica son indispensables en la contracción del músculo liso.

ABSTRACTOS DE LITERATURA MEDICA

PROPRANOLOL: PALIACION PREFERIDA PARA TETRALOGIA DE FALLOT

Garson, A., Gillette, P. C., McNamara, D. G., *Am. J. Cardiol.* 47: 1098, Mayo 1981.

Se revisaron los expedientes de 35 infantes con Tetralogía de Fallot que habían recibido propranolol para evitar los episodios hipóxicos.

Se analizaron los cineangiocardigramas para determinar si había alguna relación entre la efectividad del propranolol y la anatomía del ventrículo derecho, el infundíbulo, la arteria pulmonar, o sus ramas. No hubo relación entre la anatomía y el éxito o fracaso del medicamento.

En aquellos en que la paliación farmacológica fue efectiva se logró retrasar la cirugía un promedio de 13.1 meses. Se administró el propranolol hasta el mismo día de la cirugía y no hubo relación entre el medicamento y la mortalidad operatoria.

Los hallazgos más significativos del estudio son:

- a. que el propranolol tuvo una efectividad de 80 por ciento (28 casos).
- b. que la dosis del medicamento, y no la edad ni la anatomía, es el factor más importante en la efectividad del tratamiento.
- c. que el propranolol no afectó la mortalidad operatoria.

Los autores recomiendan el tratamiento con propranolol (2-6 mg/kg/día) para todos los infantes con episodios hipóxicos debido a la Tetralogía de Fallot.

(Sometido por Rafael Villavicencio, MD)

COMPARING RADICAL MASTECTOMY WITH QUADRANCTECTOMY, AXILLARY DISSECTION AND RADIOTHERAPY IN PATIENTS WITH SMALL CANCER OF THE BREAST

Umberto Veronesi, et al - Instituto Nazionale Tumori, Milan, Italy. *New England Journal of Medicine*, July 2, 1981 - Vol. 305, No. 1, pp. 6-11.

This is a report on a randomized trial of 701 patients with cancer of the breast of less than 2 cms. and no palpable axillary nodes. This study compared classic radical mastectomy to quadrant resection, axillary dissection and radiotherapy. 349 patients had a classical Holsted mastectomy and 362 patients had quadrantectomy.

The two groups were comparable. There were three local recurrences in the Holsted group and one in the quadrantectomy group.

Actuarial curves showed no difference in disease free and overall survival to 7 years.

The radiotherapy was to 5000 rads to the midplane of breast and 1000 rads to skin surrounding the scar.

Cosmetic results were considered satisfactory in 70 percent patients on the quadrantectomy group.

This is a significant contribution by Italian surgeons to the knowledge on breast cancer. The data shows that patients with early breast cancer (2 cms.) treated with quadrantectomy and axillary dissection and radiotherapy have the same survival, same incidence of local and distant recurrences as patients treated with Holsted mastectomy.

Although the longest follow-up is 7.5 years, it appears unlikely a longer follow-up will change results.

This article should be read by all surgeons

still doing mastectomies. Patients should be offered alternative conservative therapies.

(Submitted by Arturo A. Ydrach, MD)

ENDOSCOPIC INJECTION SCLEROSIS OF ESOPHAGEAL VARICES

Sivak, M. V., Stout, D. J., Skipper, G. - *Gastrointestinal Endoscopy* 27: 52-57, 1981.

Los autores evaluaron una nueva técnica endoscópica, la inyección de un agente esclerosante en varices esofágicas utilizando un gastroscopio flexible en pacientes conscientes pero sedados. Ninguno de los pacientes se consideró candidato quirúrgico. Todos los pacientes fueron admitidos por hemorragia de varices. Inicialmente se estabilizó la condición de los pacientes utilizando los métodos usuales (transfusión de sangre, vasopresina, etc.). La inyección de las varices se empezó de 6 a 24 horas después del comienzo de sangramiento y en tres ocasiones se inyectó durante sangramiento activo. Se repitió el procedimiento en varias ocasiones en los pacientes. Se estudiaron 22 pacientes con esta técnica. La recurrencia de sangramiento de varices y el número de transfusiones de sangre se redujo marcadamente después de las inyecciones en estos pacientes. Cuatro pacientes murieron de sangramiento de varices a pesar del tratamiento.

(Sometido por Angel Olazábal, MD)

OXYGEN DESATURATION DURING SLEEP AS A DETERMINANT OF THE "BLUE AND BLOATED" SYNDROME

A. Jayblock et al - *Gainesville, Florida - Chest*, 79: 6 June 1981.

Los pacientes con Enfermedad Obstructiva Pulmonar (COLD) se dividen frecuentemente en dos grupos:

Grupo A - Pink-puffers

Grupo B - Blue Bloaters

Cada grupo tiene unas características salientes que los diferencian superficialmente ya que la mayoría de los pacientes son una combinación de ambos tipos. Patológicamente también existe una combinación de bronquitis crónica y de enfisema.

Los autores, sin embargo, basándose en ciertas similitudes entre los "Blue Bloaters" y pacientes del síndrome Pickwickian y con el síndrome de hipersomnolencia, estudian el patrón de sueño de 10 pacientes de los cuales seis eran del tipo A-pink-puffers, cuatro eran del tipo B - Blue Bloaters.

El estudio demuestra que los pacientes clasificados como "Blue Bloaters" tenían una saturación de oxígeno arterial substancialmente más baja durante el sueño que durante las horas de vigilia en descanso. Esa hipoxemia era el resultado de 2 factores:

- a. reducción en la saturación per se.
- b. a frecuentes episodios de severa desaturación. Estos episodios eran debido a alteraciones en el patrón de la respiración. En los "pink puffers" por el contrario la reducción en la saturación de oxígeno fue solo ligera durante el período de sueño.

Los autores especulan sobre posibles causas de estas observaciones y mencionan entre otras:

- a. Diferencias en la tensiografía arterial de oxígeno inherentes a cada grupo siendo siempre más bajo en los "Blue Bloaters".
- b. Obesidad - todos los "blue bloaters" estaban sobrepeso en contraste con los "pink puffers" que pesaban menos que el peso ideal. Esto explica-

ria la hipoxemia de decúbito que ocurre en los "blue bloaters" y que se debe probablemente a una reducción del FRE (capacidad funcional residual) por debajo del CV (volumen de cierre).

- c. Respuesta ventilatoria - ciertas alteraciones en el control de la respiración durante el sueño pueden ser responsables por las diferencias en la saturación de oxígeno mientras se duermen. Esto es especialmente aplicable en la disminuída respuesta a la hipercarbia (r pCO_2) que exhiben los blue bloaters.

Los autores concluyen que sin entrar en las causas de la hipoxia la hipoxemia observada en los "Blue Bloaters" fue severa y prolongada llegando hasta el 67 por ciento del período de sueño con saturación del oxígeno de menos del 80 por ciento. Esta hipoxemia probablemente contribuye a la alta incidencia de cor pulmonale en los "Blue Bloaters" ya que la hipoxemia causa hipertensión pulmonar.

Estos resultados sugieren la necesidad de terapia de oxígeno nocturna para los "blue bloaters". Debido a las diferencias entre los gases arteriales en vigilia y en sueño los autores concluyen que basándose en los gases arteriales de día no se puede predecir el grado de hipoxemia durante el sueño.

(Sometido por R. Figueroa, MD)

EXPERIENCIA PSICOLOGICA DE PACIENTES CON DOLOR DE ESPALDA

Se pretende en este artículo explorar la experiencia psicológica de pacientes con dolor de espalda. Se asume que la experiencia de dolor, en términos generales, es función de factores constitucionales, genéticos y de aprendizaje o emocionales. Consecuentemente, aunque muchos pacientes de trauma en la región de espalda baja logran reponerse y

rehabilitarse, en otros la experiencia de dolor se integra al estilo de vida del paciente y se torna permanente o crónico. El artículo presenta ciertas características de estos pacientes de dolor crónico en términos de lo que podría llamarse el *rol de inválido*. Se exploran las causas, posible psicodinámica y factores que refuerzan o mantienen este rol en el paciente, su familia, y otros allegados. Además, se exploran las funciones que dicho estilo de vida tiene para el paciente, dentro del contexto psicológico, y se ilustran estas con presentaciones de casos. Por último, el artículo presenta y discute brevemente las implicaciones para el tratamiento de estos pacientes desde un punto de vista multidisciplinario.

TAQUICARDIA VENTRICULAR EN NIÑOS

Rocchini, A. P., Chun, P. O., Macdonald, D., *Am. J. Cardiol.* 47: 1091. May 1981.

Se evaluaron 38 pacientes con taquicardia ventricular (TV) recurrente cuyas edades fluctuaron entre 1 y 20 años. Se dividieron en dos grupos: 1) con cardiopatía asociada (21), y 2) sin cardiopatía (17).

En el grupo con cardiopatía, diecisiete presentaron síntomas (arresto cardíaco, síncope o mareos) mientras que sólo seis los tuvieron en el grupo sin cardiopatía.

Se utilizó terapia antiarrítmica en veintiocho pacientes y su eficacia se evaluó con electrocardiogramas de Holter de veinticuatro horas y pruebas de tolerancia al ejercicio.

Los hallazgos principales fueron:

1. La TV con síntomas es más frecuente en presencia de cardiopatía.
2. Hay una relación directa entre la magnitud de la TV y la presencia de síntomas.
3. La prueba de ejercicio agravó la TV en aquellos pacientes que habían presentado síntomas.

4. La terapia antiarrítmica consistió de: propranolol, fenitoína, y una combinación de ambas, dependiendo de la cardiopatía envuelta. Se recomienda terapia antiarrítmica en todos los pacientes sintomáticos, en los asintomáticos con TV mayor de 150/min. y en aquellos donde la TV se aumenta con la prueba de ejercicio.

(Sometido por Rafael Villavicencio, MD)

STUDIES ON THE MATERNAL — INFANT TRANSMISSION OF THE VIRUSES WHICH CAUSE ACUTE HEPATITIS

Tong, M. S., Thursby, M., Rakela, J. et al - Gastroenterology 80: 999-1004, 1981.

Los autores estudiaron la frecuencia de transmisión de hepatitis viral a los infantes de 83 mujeres que desarrollaron hepatitis aguda e ictericia durante el embarazo. Sesenta y cinco mujeres tuvieron hepatitis tipo B. Solo uno de los 33 infantes nacidos de madres que tuvieron hepatitis B durante el primer o segundo trimestre se infectó con el virus. En las 24 madres con hepatitis en el tercer trimestre se transmitió el virus a 16 infantes. Ocho madres tuvieron hepatitis postpartum (hasta 6 semanas después) y los ocho infantes nacidos se infectaron. De los 25 infantes infectados con hepatitis tipo B, 24 desarrollaron la evidencia de infección (antígeno de superficie presente en el suero) de 4 a 16 semanas de edad (uno solamente tenía el antígeno al nacer), dos desarrollaron ictericia y recobraron completamente, y 23 han persistido con el antígeno de superficie presente y con elevaciones intermitentes de las transaminasas. Seis madres desarrollaron hepatitis de tipo A. Ninguno de los infantes nacidos de estas madres desarrollaron evidencia de hepatitis.

Doce madres tuvieron hepatitis tipo no-A, no-B, y en seis de los infantes hubo evidencia de infección.

Los autores mencionan en su discusión de los posibles beneficios que terapia inmunológica puede ofrecer a los infantes nacidos de madres con hepatitis viral.

(Sometido por Angel Olazábal, MD)

QUALITY OF LIFE IN BENEFIT-COST ANALYSES OF REHABILITATION RESEARCH

David Caudús, MD, Marcus J. Futhreu, PhD, Robert M. Thrall, PhD - Archive of PM&R 62-209-212, 1981.

Tradicionalmente, modelos con beneficio de costo han sido limitados a la consideración de beneficios monetarios. Este acercamiento ha sido motivado por el hecho de que los beneficios no monetarios son difíciles de definir y cuantificar. Derivado de la teoría general de el análisis de Beneficios de Costos, se describe un modelo el cual incluye 3 categorías de beneficio, identificados por un procedimiento como "Delphi"; administrado a un grupo representacional de personas envueltas en el proceso de Rehabilitación. Mientras que los beneficios monetarios tienen el dólar disponible como unidad de medida; escalas de beneficios no monetarios deben ser desarrollados. Los invitados para estimar los valores y la importancia relativa de los beneficios se analizan y se propone un procedimiento para combinar beneficios monetarios y no monetarios.

(Sometido por Edgar Baucage, MD)

ACUPUNTURA EN DOLOR DE EXTREMIDADES FANTASMAS

Trilok N. Monga, MD, Tom Jaksic, BS - Archives of PM&R, 62: 229-231, 1981.

Un caso de un paciente varón de 36 y/o, con un historial de amputación traumática debajo del codo en el lado izquierdo resultando en dolor intractable en la extremidad fantasma antes descrita. El paciente falló en responder a una variedad de medicamentos incluyendo varios analgésicos, tranquilizantes, y bloqueadores Beta; otras series de modalidades de tratamiento convencionales, las cuales incluían el bloqueo del ganglio estrellado o nervios periferales e incisión neuronal con la transposición anterior del nervio ulnar no resolvieron el dolor. La acupuntura fue entonces establecida con un alivio subjetivo del dolor de la extremidad fantasma y el resultado objetivo de que el paciente pudiera usar una prótesis.

(Sometido por Edgar Baucage, MD)

ETIOLOGY OF ACUTE CONJUNCTIVITIS IN CHILDREN

Gigliotti, F., Williams, W. T., Hayden, T.G., Owen, H., et al: J. Pediatr. 98: 531, 1981.

Acute conjunctivitis is common in ambulatory pediatric practice but the etiology is usually

not determined.

The present study was undertaken to determine the etiology of acute conjunctivitis in children seen in ambulatory practice in the United States. Culture techniques designed to detect respiratory viruses, *C. trachomatis* and aerobic bacteria were employed.

Ninety nine patients with conjunctivitis and 102 age and season matched controls were cultured. The mean ages of the patients and the controls were 4.4 and 4.9 years respectively. Agents statistically associated with conjunctivitis included *H. influenzae* (42 percent vs 0 percent), *Streptococcus pneumoniae* (12 percent vs 3 percent) and adenoviruses (20 percent vs 0 percent). One of these three etiologic agents was isolated from 72 percent of the patients. Simultaneous infections with two pathogens was uncommon.

Staphylococcus aureus was equally prevalent in diseased and control eyes, one strain of *C. trachomatis* was isolated from control eyes. Differentiation of viral and bacterial conjunctivitis in an individual patient was difficult.

An adenovirus was isolated from 11 (65 percent) of 17 patients who had pharyngitis in addition to conjunctivitis. *H. influenzae* was isolated from 14 (74 percent) of 19 children who had both otitis and conjunctivitis. Adenovirus conjunctivitis was common in the Fall and *H. influenzae* in Winter.

CURSOS

CLINICAL CYTOPATHOLOGY FOR PATHOLOGISTS POSTGRADUATE COURSE

The Twenty-third Postgraduate Institute for Pathologists in Clinical Cytopathology is to be given at The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore, Maryland, March 22-April 2, 1982. The full two week program is designed for pathologists who are Certified (or qualified) by the American Board of Pathology (PA), or its international equivalent.

It will provide an intensive refresher in all aspects of the field of Clinical Cytopathology, with

time devoted to newer techniques, special problems, and recent applications. Topics will be covered in lectures, explored in small informal conferences, and discussed over the microscope with the Faculty. Self-instructional material will be available to augment at individual pace. A loan set of slides with text will be sent to each participant for home-study during February and March before the Institute. Credit hours 125 in AMA Category I.

Application is to be made before January 27, 1982. For details, write: John K. Frost, MD, 610 Pathology Building, The Johns Hopkins Hospital, Baltimore, Maryland 21205, U. S. A.

The entire Course is given in English.

NOTICIAS

AMA NEWS:

MARIJUANA INGREDIENT OKAYED TO AID CANCER SUFFERERS

CHICAGO — The National Cancer Institute (NCI) recommends that the active ingredient in marijuana, delta-9-tetrahydrocannabinol (THC), be made available to cancer patients who suffer from severe nausea and vomiting associated with chemotherapy, according to a report in the *Journal of the American Medical Association* (May 22).

In 6 out of 7 studies involving 389 patients, THC was superior in treating cancer patients who were not helped by standard anti-nausea drugs, the NCI reports. In one study, THC was found equal to a major tranquilizer in effectiveness.

THC's action against nausea and vomiting was most pronounced when patients experienced a "high". A high can begin 20 to 60 minutes after the drug is taken and can last from one to five hours.

The high associated with THC involves mood changes (easy laughing, elation and heightened awareness), mildly disordered fine motor coordination and some distortion of activities and interactions with others. Sleepiness was another common side effect.

A few patients exhibited more severe consequences, including visual hallucinations, anxiety and depression, coordination problems, abnormal sensations, rapid heart rate and low blood pressure.

Although the studies used orally administered THC, the NCI reports that inhaling the drug is a more reliable way of introducing it into the blood. Many patients, however, dislike the taste of smoked marijuana or may not be familiar with smoking. Also, smoking marijuana could impair airway or lung status in an already compromised patient.

Still, the NCI states that for the group of patients in which smoking poses few problems, marijuana cigarettes could be an effective substitute for

the orally administered drug. They recommend more studies in this area.

Certain cancer patients should receive THC only after careful consideration and under strict supervision, the NCI advises. These include mentally ill patients, who might be compromised by THC-induced anxiety and depression; epileptic patients, because THC enhances seizure activity; patients who want to become or are pregnant, because THC is toxic to embryos; patients with cardiac problems or impaired liver function; elderly patients; and patients taking other psychoactive drugs.

AMA TO OFFER LANGUAGE STUDY FOR FOREIGN-TRAINED PHYSICIANS

CHICAGO — The American Medical Association next fall will offer an intensive one-day course on improving English pronunciation for foreign physicians.

The course is designed to assist foreign physicians now in practice in the United States in improving spoken communications with their patients.

Sessions will be held Saturday, September 12, at New York Academy of Medicine in New York City. Physicians attending will receive formal credits in continuing medical education.

The course will be taught by Mrs. Elizabeth Lang, professor of English as a second language, Cuyahoga Community College, Cleveland, Ohio. Mrs. Lang has developed a study manual and cassette tapes for home study.

There will be lectures and practice on producing the sounds of general American English, in-

tensive oral drill and criticism of individual students, and practice in sustained discourse through reading and extemporaneous speaking.

The course is limited to 20 students. If it is oversubscribed by as many as 10, an additional course will be held on Sunday, September 13.

Further information on the course is available from Henry Mason, Division of Professional Relations, AMA, 535 N. Dearborn St., Chicago, Il. 60610. Course director is Mortimer Enright, head of the AMA's Speakers and Leadership Program Section.

UNDUE DELAYS CITED IN RECOGNIZING NEW TREATMENT FOR PSORIASIS

CHICAGO — Five years ago a new form of treatment for psoriasis was introduced and has proved highly effective for more than 40,000 patients in the United States, with a bare minimum of untoward side effects.

And yet the Food and Drug Administration still has not licensed the treatment and thus sufferers are denied payment of medical costs by Medicare, Medicaid and some private health insurance companies, a Chicago doctor charges.

In an editorial in the May 15 Journal of the American Medical Association, Henry H. Roenigk, MD, of Northwestern University Medical School, Chicago, points out that "All drugs entail risks, but the FDA cannot create a riskless society by playing it safe" and stalling for years on new drug applications.

There have been some hints that the treatment might cause skin cancers, but large scale scientific tests have shown that there is no more risk of skin cancer from the new treatment than from other FDA-approved systemic therapy for psoriasis, Dr. Roenigk says.

The new treatment is called PUVA. It combines taking a medicine called methoxsalen, followed by exposure to long wave ultra violet light (UVA) in special phototherapy boxes in established centers.

It has proved highly effective in two large cooperative studies in the United States and also has been confirmed as standard therapy worldwide, Dr. Roenigk says.

Methoxsalen is available to doctors on prescription for treatment of another type of skin problem, vitiligo. UVA lights also may be purchased by the doctor. Most institutions using the treatment have been granted Investigational New Drug (IND) permits for PUVA by the FDA. This makes its use legal as an experimental procedure, but it does not qualify for most insurance payments. More than 100 centers have the IND permits.

PUVA therapy has been considered by the FDA in at least five separate Dermatology Advisory Board meetings over the past three years. Approval has been withheld primarily because of concern for potential long-term side effects, Dr. Roenigk says.

In the same issue of the Journal is a report from a Harvard Medical School study of impact of PUVA treatment on cost of psoriasis treatment in general.

Robert S. Stern, MD, and colleagues documented the cost of treatment for 1,320 patients with regard to hospitalization and cost of PUVA treatments.

Within the one-year period before initiation of PUVA, average hospital days per person per year were 5.1 for psoriasis sufferers. After PUVA treatments were begun, average hospital stay dropped off to 1.2 days. Cost of the PUVA treatments largely offset the saving in hospitalization, Dr. Stern says. But the new treatment does not substantially increase the overall cost of treatment, he declares.

PENICILLIN ALLERGY RARER THAN SUSPECTED

CHICAGO — Most people who think they are allergic to penicillin actually aren't, says a report in the May 22/29 Journal of the American Medical Association.

As many as 10 to 15 percent of individuals checking into hospitals say they have had a previous reaction to penicillin. But when skin tests to determine allergy are conducted only one-fourth or less actually are allergic.

This doesn't mean they did not once have an allergic reaction to the antibiotic. It means that the allergy has faded away with the passage of time, and it is now safe to administer the drug that fights bacterial infection.

In the May 22/29 Journal of the American Medical Association, N. Franklin Adkinson, Jr., MD, of the Johns Hopkins University School of Medicine, Baltimore, tells of a study that sought to find when some individuals lose their allergy to penicillin.

Dr. Adkinson reports that he learned some facts about the speed at which penicillin allergy regresses, but could not find out why it happens.

Another study by Bernard Levine, MD, of New York University, indicates that up to 90 percent of persons with histories of penicillin allergy have negative results when skin-tested.

The National Institute of Allergy and Infectious Diseases is now extending Dr. Levine's investigation to eight different centers.

The report is in the Medical News Section of the Journal.

NEWS — HOME STUDY COURSES AVAILABLE FROM UNIVERSITY OF WISCONSIN

MADISON — The University of Wisconsin announces the availability of home study courses in Hematology, Hypertension, Immunology, Infectious Diseases, Neuropharmacology, and Pharmacology. Courses may be ordered at any time and completed at the physician's own pace. Completion of a course earns from 20 - 45 hours of ACCME Category I continuing education credit.

For further information contact: Home

Study —CME, University of Wisconsin, 481 WARF Building, 610 Walnut St., Madison, WI 53706.

The American Medical Association's popular pamphlet, YOUR BLOOD PRESSURE, points out that uncontrolled elevated blood pressure will harm your vital organs. The heart, arteries, brain, kidneys and eyes may be affected by hypertension. Because no warning signs or symptoms are likely to appear to signal the effects of high blood pressure, organ failure can begin without your knowing it.

The heart is the organ most commonly damaged by high blood pressure. The higher the pressure, the harder the heart must work. In response to increased effort, the heart muscle itself increases in size. Then the diagnosis is hypertensive heart disease. Eventually the enlarged heart becomes unable to meet the demands placed on it and congestive heart failure occurs.

Hypertension also contributes to atherosclerosis (fatty deposits in the arterial walls). When this occurs in the coronary arteries, they become narrowed. The blood supply to the heart muscle diminishes, and this change may result in chest pain on exercise (angina pectoris) or even in serious injury to part of the heart muscle (heart attack).

The large arteries that carry blood from the heart to body tissues are another major target of high blood pressure. Damage to these arteries often takes the form of arteriosclerosis, which narrows them considerably and reduces their capacity to carry blood.

Brain may be affected

Persistent high blood pressure may affect the brain by leading to a stroke. This happens when a cerebral artery becomes critically narrowed due to atherosclerosis or when continued increased pressure weakens the artery until a blood clot occurs or the artery ruptures, producing a brain hemorrhage.

Hypertension reduces kidney function by damaging the arterioles that supply the kidneys with blood. The kidneys eventually become unable to rid the body of waste products and kidney failure results.

Eyes, too, are affected. If the condition is left unchecked, blood vessels in the eye become increasingly abnormal. This can lead to blindness. The physician can assess the amount of vascular damage in the whole body by checking the blood vessels in the eyes.

In untreated hypertension, the time from onset to death is about 20 years. Except for an elevated blood pressure reading, no warning signs or symptoms are likely to appear for the first two thirds of this time, after which failure of one or more vital organs occurs. Once organ failure begins, the average survival of the untreated patient is about six years.

Blood pressure explained

Okay. So high blood pressure is serious. Just what is blood pressure, anyway?

Your heart and blood vessels make up your body's distribution (circulatory) system, upon which all life processes depend. Under pressure, your blood carries food and oxygen to and removes waste products from every cell in your body.

Blood pressure is maintained by your heart that acts as a pump, thick-walled arteries that distribute blood to body organs, and small arterioles that empty into capillaries (tiny blood vessels). The capillaries deliver blood in a smooth flow directly to your tissues.

Blood is returned to your heart through your veins and is forced through your lungs where it picks up a fresh supply of oxygen and eliminates waste gas (carbon dioxide). It then flows to the left side of your heart and is ready for another trip through your body.

The arterioles, muscular tubes that connect the arteries and capillaries, regulate your blood pressure. When an arteriole contracts, the force of blood (blood pressure) against the vessel walls builds up behind it. Most cases of high blood pressure are related in some way to faulty functioning of the arte-

rioles.

Thus, to repeat, blood pressure is the force exerted by blood against the walls of the vessels that carry it. Generally, the blood pressure in the arteries varies as the heart pumps: 1) when the heart contracts, the pressure is increased (systolic pressure); 2) when the heart relaxes between contractions, the pressure is decreased (diastolic pressure).

How pressure is measured

Blood pressure is measured by an instrument called a sphygmomanometer (Greek for pulse measurement). An inflatable, bag-like cuff is wrapped around your arm above the elbow. A tube connects this cuff to a measuring device that contains a column of mercury (a barometer). The cuff is inflated until the main artery in your arm is squeezed tightly enough to shut off the flow of blood. Placing a stethoscope over the artery, the physician slowly deflates the cuff.

As pressure against the artery is reduced, he reads the height of the column of mercury when the pulse sound can first be heard. This is your systolic pressure (maximum pressure in the arteries when the heart is contracting). Continuing to deflate the cuff, he takes another reading when the pulse sound disappears. This is your diastolic pressure (minimum pressure maintained in the arteries between heart beats).

The physician records the numbers that represent both the systolic and diastolic pressures each time he measures your blood pressure. He writes the numbers this way: 155/100. This is the systolic pressure/diastolic pressure. The physician will say to you: "Your blood pressure is 155/100."

A pressure of 110/60 to 140/90 is usually considered within normal limits, depending on the state of your health. When pressure rises above 140/90, it may adversely affect your health. Because occasional increases are fairly common, more than one reading is required before a diagnosis is made.

Low Pressure not a problem

Sometimes the physician finds you have low blood pressure. Except in rare cases of shock, low blood pressure is not harmful and can even mean a

longer life.

High blood pressure usually begins at about 30 years of age and becomes increasingly common the older one gets, but it is sometimes found even in children. It can occur at any age and in any person.

High blood pressure occurs more frequently in men than in women, and in women is often associated with birth control pills or pregnancy. It occurs more frequently in blacks than in whites, in obese people, and in relatives of people with high blood pressure. Factors involved in the disorder are heredity, obesity, excessive salt intake, and a stressful lifestyle.

High blood pressure usually is detected during a routine physical examination. In at least 90 percent of those with hypertension, no underlying

disorder can be found, and these people are said to have "essential hypertension."

To control high blood pressure so that damage to vital organs is prevented, the physician may prescribe medication and urge the patient to lose weight, reduce his intake of salt, to curtail cigarette smoking and use of alcohol, and to adjust his lifestyle to reduce emotional strain.

The National High Blood Pressure Education Program was started in 1972 to create public awareness about high blood pressure. The program is under the direction of the National Heart, Lung and Blood Institute of the National Institutes of Health, in cooperation with 15 federal agencies, 150 national voluntary organizations and almost every state health department.

ANUNCIO

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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML



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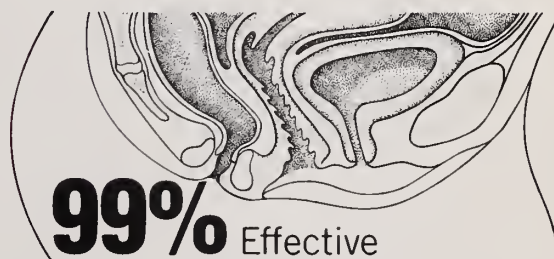
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A study of 59 patients with symptomatic upper urinary tract infection showed that Septra achieved 91.5% bacteriologic cure rate[‡] when evaluated up to seven days post-therapy. Of the 53 patients available for follow-up, 96.2% maintained bacteriologic cure from one to four weeks post-therapy.⁴

In another study of 172 patients, many with recurrent cystitis, Septra achieved a 99.7% bacteriologic cure[‡] at end of therapy; 72.7% cure up to 18 days post-therapy.⁴

In the laboratory: Septra is effective against susceptible strains of *E. coli*, *Klebsiella*, *Enterobacter* and *Proteus*.[§]

PRESCRIBING CONSIDERATIONS: Septra is contraindicated during pregnancy and the nursing period, in patients hypersensitive to its components, and in infants under 2 months. During therapy maintain adequate fluid intake, perform frequent CBCs and urinalyses with microscopic examination.

*due to susceptible organisms

†tissue levels do not necessarily correspond to clinical effectiveness

‡10,000 or fewer organisms/ml urine

§*In vitro* data do not necessarily correlate with clinical results.

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*due to susceptible organisms

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INDICATIONS AND USAGE:

URINARY TRACT INFECTIONS: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

NOTE: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of these urinary tract infections.

ACUTE OTITIS MEDIA: For the treatment of acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in the judgment of the physician, Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to *Haemophilus influenzae* resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: For the treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *Haemophilus influenzae* and *Streptococcus pneumoniae* when in the judgment of the physician, Septra offers some advantage over the use of a single antimicrobial agent.

SHIGELLOSIS: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

PNEUMOCYSTIS CARINII PNEUMONITIS: Septra is also indicated in the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period (see "Reproduction Studies"). Infants less than two months of age.

WARNINGS: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A, β -hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but it has been reported to interfere with hematopoiesis in occasional patients. In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombopenia with purpura has been reported.

The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts should be done frequently in patients receiving Septra. If a significant reduction in the count of any formed blood element is noted, Septra should be discontinued.

PRECAUTIONS: Septra should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

It has been reported that Septra may prolong the prothrombin time of patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when Septra is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

ADVERSE REACTIONS: For completeness, all major reactions to sulfonamides and to trimethoprim are included below even though they may not have been reported with Septra.

Blood Dyscrasias: Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia.

Allergic Reactions: Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

Gastrointestinal Reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis.

C.N.S. Reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

Miscellaneous Reactions: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarthritis nodosa and L.E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Goiter production, diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, ACUTE OTITIS MEDIA IN CHILDREN AND ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS.

Adults: The usual adult dosage for the treatment of urinary tract infections and acute exacerbations of chronic bronchitis is one Septra DS Tablet every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. In children weighing 88 lbs (40 kg) or more, the dosage is one Septra DS Tablet every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15-30	Half of the usual dosage regimen
Below 15	Use Not Recommended

PNEUMOCYSTIS CARINII PNEUMONITIS:

The recommended dosage for patients with documented *Pneumocystis carinii* pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. In children weighing 70 lbs (32 kg) or more, the dosage is one Septra DS Tablet every 6 hours for 14 days.

HOW SUPPLIED: Oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole — bottle of 100, unit dose pack of 100 and COMPLIANCE™ Pak of 20.

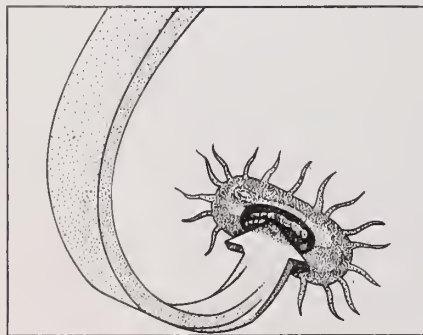
Also available in regular tablets containing 80 mg trimethoprim and 400 mg sulfamethoxazole (bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100) and oral suspension containing 40 mg trimethoprim and 200 mg sulfamethoxazole in each 5 ml (bottle of 473 ml. Unit of Use: bottle of 100 ml with child-resistant cap).

Reproduction Studies: In rats, doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palate. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In rabbits, trimethoprim administered by intubation from days 8 to 16 of pregnancy at dosages up to 500 mg/kg resulted in higher incidences of dead and resorbed fetuses, particularly at 500 mg/kg. However, there were no significant drug-related teratological effects.

REFERENCES: 1. Kucers A, Bennett N Mck: *The Use of Antibiotics: A Comprehensive Review with Clinical Emphasis*, ed 3. Philadelphia, Lippincott, 1979, p 700. 2. Stamey TA, Condy M: The diffusion and concentration of trimethoprim in human vaginal fluid in *Trimethoprim/Sulfamethoxazole: A Compilation of Clinical and Pharmacodynamic Studies in Chronic and Recurrent Urinary Tract Infection*. New York, Science & Medicine, 1975, p 13. 3. Naff H: On the changes in the intestinal flora induced in man by Bactrim®. *Path Microbiol* 37: 1, 1971. 4. Data on file, Burroughs Wellcome Co.

†Mfd. under Pat. #3,956,327



Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

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AT THE AMERICAN MEDICAL ASSOCIATION
WE'RE INVOLVED IN MEETING
THE IMPORTANT CHALLENGES AND
RESPONSIBILITIES OF THE 80'S
This is another in a series of reports on
major issues facing the medical profession. The purpose is to
inform physicians and medical students on what the AMA is
doing, on behalf of the profession and the public, to influence
decisions that will affect health care in the next decade and beyond.

ESTABLISHING MEDICAL ETHICS FOR A CHANGING PROFESSION

As a physician or medical student, you automatically have a strong vested interest in medical ethics. Ethics are a traditional frame of reference for society's attitude toward physicians. Today in America, there is more reference to that frame than ever before.

That's because so many of today's health-care issues are ethical challenges. As outstanding examples, consider the moral right and wrong involved in:

- Seemingly excessive or needless costs of medical services—at a time when cost is the chief health-care issue and the chief basis for government intervention in care.
- Medicine's enhanced ability and obligation to prolong the lives of the terminally ill—versus pressures for mercy killing and for limits on the expenditure of health-care resources.
- Rules and procedures that could make medical records more accessible to outsiders. The moral conflict here is between the principles of confidentiality and the stake of third parties (notably government) in medical oversight and review.
- The question as to where various biomedical advances, such as genetic engineering and test-tube fertilization will lead us?

Those and similar questions involve the very character of

medical practice, including your own. Ethically wrong answers could distort that character.

Physicians have to do their best to provide answers that are both high-minded and sure-footed. Acting in concert, we have to come forth with sound ethical principles and applications.

The AMA has stood for traditional moral values from its very beginnings but has been flexible enough to keep adapting to new needs. In order to adapt, the AMA (by vote of its House of Delegates) revised its Principles of Medical Ethics last July—the fifth time it has done so.

Here are some of the ways in which the AMA has been applying medical ethics to relevant current issues . . . on your behalf:

- Stimulation of ways to cut down on needless or excessive health services and costs. This includes peer and utilization review, physician participation in PSROs, cost-benefit analysis, and alternatives to hospitalization whenever feasible.
- Model state legislation for disciplining the wayward or incompetent physician, who can be an economic as well as a medical problem. Twenty-three states now have laws that wholly or partially resemble the AMA model.
- New ethical standards on such topics as genetic engineering, test-tube fertilization, and euthanasia . . . as set forth in the latest edition of the AMA Judicial Council Opinions and Reports.
- Tireless legislative and legal efforts to protect the confidentiality of patient records.
- To maximize our effectiveness, we need YOUR MEMBERSHIP. The larger our membership (230,000 now), the bigger our influence. We need influence in coordinating the ethical commitment of American medicine . . . and in clarifying that commitment to government, to society, and throughout our profession.

We need YOU . . . if we're to give you all the help that you need.

For details on how to join, contact your state or county medical society or the Office of Membership Development, American Medical Association, 535 N. Dearborn, Chicago, IL 60610 (312) 751-6410.

Valium[®] diazepam/Roche

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety; symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome. *Oral form* may be used adjunctively in convulsive disorders, but not as sole therapy. *Injectable form* may also be used adjunctively in: status epilepticus; severe recurrent seizures; tetanus; anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindications: Tablets in children under 6 months of age; known hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of predisposition to habituation/dependence.

Use in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or become pregnant.

ORAL: Advise patients against simultaneous ingestion of alcohol and other CNS depressants.

Not of value in treatment of psychotic patients; should not be employed in lieu of appropriate treatment. When using oral form adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may be associated with temporary increase in frequency and/or severity of seizures.

INJECTABLE: To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist, use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest, concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea, have resuscitative facilities available. When used with narcotic analgesic eliminate or reduce narcotic dosage at least 1/3, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status. Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), i.e., phenothiazines, narcotics, barbiturates, MAO inhibitors and antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function, avoid accumulation in patients with compromised kidney function. Limit oral dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

INJECTABLE: Although promptly controlled, seizures may return, re-administer if necessary; not recommended for long-term maintenance therapy. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue, ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo; blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, discontinue drug.

Because of isolated reports of neutropenia and jaundice, periodic blood counts, liver function tests advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium (diazepam/Roche) therapy and are of no known significance.

INJECTABLE: Venous thrombosis/phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat or chest have been reported.

Dosage: Individualized for maximum beneficial effect.

ORAL—Adults: Anxiety disorders, relief of symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; acute alcohol withdrawal, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

INJECTABLE: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V., and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, administer I.V. slowly; for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary, in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. **Infants (over 30 days) and children (under 5 years),** 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). **Children 5 years plus,** 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure, if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure, employ general supportive measures, I.V. fluids, adequate airway. Use levaterenol or metaraminol for hypotension. Dialysis is of limited value.

Supplied: Tablets, 2 mg, 5 mg and 10 mg, bottles of 100 and 500, Tel-E-Dose[®] (unit dose) packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10. Prescription Paks of 50, available in trays of 10. Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1, Tel-E-Ject[®] (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam, compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.



ROCHE LABORATORIES
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Examine Me.

During the past several years, I have heard my name mentioned in movies, on television and radio talk shows, and even at Senate subcommittee sessions. And I have seen it repeatedly in newspapers, magazines, and yes, best-sellers. Lately, whenever I see or hear the phrases "overmedicated society," "overuse," "misuse" and "abuse," my name is one of the reference points. Sometimes even *the* reference point.

These current issues, involving patient compliance or dependency-proneness, should be given careful scrutiny, for they may impede my overall therapeutic usefulness. As you know, a problem almost always involves improper usage. When I am prescribed and taken correctly, I can produce the effective relief for which I am intended.

Amid all this controversy, I ask you to reflect on and re-examine my merits. Think back on the patients in your practice who have been helped through your clinical counseling and prudent prescriptions for me. Consider your patients with heart problems, G.I. problems and interpersonal problems who, when their anxiety was severe, have been able to benefit from the medication choice you've made. Recall how often you've heard, as a result, "Doctor, I don't know what I would have done without your help."

You and I can feel proud of what we've done together to reduce excessive anxiety and thus help patients to cope more successfully.

If you examine and evaluate me in the light of your own experience, you'll come away with a confirmation of your knowledge that I *am* a safe and effective drug when prescribed judiciously and used wisely.







